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(54) Title: NOVEL BAG PROTEINS AND NUCLEIC ACID MOLECULES ENCODING THEM

(57) **Abstract**

The present invention provides a family of BAG–1 related proteins from humans (BAG–1L, BAG–1, BAG–2, BAG–3, BAG–4 and BAG–5), the invertebrate *C. elegans* (BAG–1, BAG–2) and the fission yeast *S. pombe* (BAG–1A, BAG–1B) and the nucleic acid molecules that encode them.

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BNSDOCID <WO 0014106A1 1 >

NOVEL BAG PROTEINS AND NUCLEIC ACID MOLECULES ENCODING THEM

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BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

This invention relates generally to the fields of molecular biology and molecular medicine and more specifically to a novel family of proteins that can regulate protein folding. The functions of these proteins are potentially diverse, including promoting tumor cell growth and metastasis.

BACKGROUND INFORMATION

The Hsc70/Hsp70-family of molecular chaperones participate in protein folding reactions, controlling protein bioactivity, degradation, complex assembly/disassembly, and translocation across membranes. These proteins interact with hydrophobic regions within target proteins via a carboxyl (C)-terminal peptide binding domain, with substrate binding and release being controlled by the N-terminal ATP-binding domain of Hsc70/Hsp70. Hsc70/Hsp70-assisted folding reactions are accomplished by repeated cycles of peptide binding, refolding, and release,

which are coupled to ATP hydrolysis by the ATP-binding domain (ATPase) of Hsc70/Hsp70 and by subsequent nucleotide exchange. The chaperone activity of mammalian Hsc70/Hsp70 is regulated by partner proteins that either modulate the peptide binding cycle or that target the actions of these chaperones to specific proteins and subcellular compartments. DnaJ-family proteins (Hdj-1/Hsp40; Hdj-2; Hdj-3) stimulate the ATPase activity of Hsc70/Hsp70, resulting in the ADP-bound state which binds tightly to peptide substrates. The Hip protein collaborates with Hsc70/Hsp70 and DnaJ homologues in stimulating ATP hydrolysis, and thus also stabilize Hsc70/Hsp70 complexes with substrate polypeptides, whereas the Hop protein may provide co-chaperone functions through interactions with the C-terminal peptide binding domain.

The Bcl-2 associated athanogene-1 (bag-1) is named from the Greek word *athanos*, which refers to anti-cell death. BAG-1 was previously referred to as Bcl-2-associated protein-1 (BAP-1) in U.S. Patent No. 5,539,094 issued July 23, 1996, which is incorporated herein by reference. In this earlier patent, BAG-1 is described as a portion of the human BAG-1 protein, absent the N-terminal amino acids 1 to 85. In addition, a human protein essentially identical to human BAG-1 was described by Zeiner and Gehring, (*Proc. Natl. Acad. Sci., USA* **92**:11465-11469 (1995)). Subsequent to the issuance of U.S. Patent 5,539,094 the N-terminal amino acid sequence from 1 to 85 of human BAG-1 was reported.

BAG-1 and its longer isoforms BAG-1M (Rap46) and BAG-1L are recently described Hsc70/Hsp70-regulating proteins. BAG-1 competes with Hip for binding to the Hsc70/Hsp70 ATPase domain and promotes substrate release. BAG-1 also reportedly stimulates Hsc70-mediated ATP

BNSDOCID <WO_0014106A1_I_>

hydrolysis by accelerating ADP/ATP exchange, analogous to the prokaryotic GrpE nucleotide exchange protein of the bacterial Hsc70 homologue, DnaK. Gene transfection studies indicate that BAG-1 proteins can influence a wide variety of cellular phenotypes through their interactions with Hsc70/Hsp70, including increasing resistance to apoptosis, promoting cell proliferation, enhancing tumor cell migration and metastasis, and altering transcriptional activity of steroid hormone receptors.

Despite the notable progress in the art, there remains an unmet need for the further identification and isolation of additional homologous BAG protein species, and the nucleic acid molecules and/or nucleotide sequences that encode them. Such species would provide additional means by which the identity and composition of the BAG domain, that is, the portion of the protein that is influencing or modulating protein folding, could be identified. In addition, such species would be useful for identifying agents that modulate apoptosis as candidates for therapeutic agents, in particular, anticancer agents. The present invention satisfies these need, as well as providing substantial related advantages.

SUMMARY OF THE INVENTION

The present invention provides a family of BAG-1 related proteins from humans [BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO: 4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22) and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24)] , the invertebrate *C.elegans* [BAG-1 (SEQ ID NO:12), BAG-2 (SEQ ID NO:14)] and the fission yeast *S.pombe* [BAG-1A (SEQ ID NO:16), BAG-1B (SEQ ID NO:18)] and the nucleic acid molecules that encode them.

Another aspect of the present invention provides an amino acid sequence present in the family of BAG-1 related proteins, that modulates Hsc70/Hsp70 chaperone activity, that is, the BAG domain.

Another aspect of the present invention provides novel polypeptide and nucleic acid compositions and methods useful in modulating Hsc70/Hsp70 chaperone activity.

Another aspect of the present invention is directed to methods for detecting agents that modulate the binding of the BAG family of proteins, such as BAG-1 (beginning at residue 116 of SEQ ID NO:2), and related proteins with the Hsc70/Hsp70 Family of proteins or with other proteins that may interact with the BAG-Family proteins.

Still another aspect of the present invention is directed to methods for detecting agents that induce the dissociation of a bound complex formed by the association of BAG-Family proteins with Hsc70/Hsp70 Family molecule chaperones or other proteins.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the full length cDNA sequence for human BAG-1 (SEQ ID NO:1) protein with the corresponding amino acid sequence (SEQ ID NO:2). Within the full length sequence are included the overlapping sub-sequences of BAG-1 (beginning at nucleotide 391), BAG-1M [beginning at nucleotide 260 of (SEQ ID NO:2)], and BAG-1L [beginning at nucleotide 46 of (SEQ ID NO:2)].

BNSDOCID <WO 0014106A1 >

Figures 2A and 2B combined shows the full length cDNA sequence (SEQ ID NO:3) aligned with the corresponding amino acid residues for human BAG-2 protein (SEQ ID NO:4).

Figure 3 shows a cDNA sequence (SEQ ID NO:5) aligned with the corresponding amino acid residues for human BAG-3 protein (SEQ ID NO:6).

Figure 4 shows the a cDNA sequence (SEQ ID NO:7) aligned with the corresponding amino acid residues for human BAG-4 protein (SEQ ID NO:8).

Figure 5 shows a cDNA sequence (SEQ ID NO:9) aligned with the corresponding amino acid residues for human BAG-5 protein (SEQ ID NO:10).

Figure 6A shows the full length cDNA sequence for *C. elegans* BAG-1 protein (SEQ ID NO:11).

Figure 6B shows the 210 amino acid sequence for *C. elegans* BAG-1 protein (SEQ ID NO:12).

Figure 7A shows the full length cDNA sequence for *C. elegans* BAG-2 protein (SEQ ID NO:13).

Figure 7B shows the 458 amino acid sequence for *C. elegans* BAG-2 protein (SEQ ID NO:14).

Figure 8A shows the full length cDNA sequence for *S. pombe* BAG-1A protein (SEQ ID NO:15).

Figure 8B shows the 195 amino acid sequence for *S. pombe* BAG-1A protein (SEQ ID NO:16).

BNSDOCID <WO 0014106A1 >

Figure 9A shows the full length cDNA sequence for *S. pombe* BAG-1B protein (SEQ ID NO:17).

Figure 9B shows the 206 amino acid sequence for *S. pombe* BAG-1B protein (SEQ ID NO:18).

Figure 10 shows the topologies of the BAG-family proteins; human BAG proteins, BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), BAG-4 (SEQ ID NO:8), BAG-5 (SEQ ID NO:10); *S.pombe* BAG-1A (SEQ ID NO:16)and BAG-1B (SEQ ID NO:18); and *C. elegans* BAG-1 (SEQ ID NO:12)and BAG-2 (SEQ ID NO:14). (A) The relative positions of the BAG domains are shown in black, ubiquitin-like regions are represented in gray, WW domain are represented in strips. Nucleoplasmin-like nuclear localization sequence are also shown. (B) The amino acid sequences of the BAG domain for human BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), BAG-4 (SEQ ID NO:8), BAG-5 (SEQ ID NO:10), *S.pombe* BAG-1A (SEQ ID NO:16)and BAG-1B (SEQ ID NO:18), and *C. elegans* BAG-1 (SEQ ID NO:12)and BAG-2 (SEQ ID NO:14) are aligned demonstrating their homology. Black and gray shading represent identical and similar amino acids, respectively.

Figure 11 shows assays demonstrating the interaction of BAG-family proteins with Hsc70/ATPase. (A) Two-hybrid assays using yeast expressing the indicated fusion proteins. Blue color indicates a positive interaction, resulting in activation of the *lacZ* reporter gene. (B) *In vitro* protein assays using GST-fusion proteins and ^{35}S-labeled *in vitro* translated proteins. (C) Co-immunoprecipitation assays using anti-Flag or IgG1 control antibodies and lysates from 293T cells expressing Flag-tagged BAG-1 (beginning at residue 116 of SEQ ID

BNSDOCID <WO 0014106A1 | >

NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), Daxx, or Apaf-1.

Figure 12 shows surface plasmon resonance analysis of BAG-family protein interactions with Hsc70/ATPase. (A) SDS-PAGE analysis of purified recombinant proteins. (B) Representative SPR results of biosensor chips containing immobilized BAG proteins with and without maximally bound Hsc70/ATPase.

Figure 13 shows representative SPR results for biosensor chips containing immobilized BAG-1 (beginning at residue 116 at SEQ ID NO:2), BAG-1(ΔC), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) proteins. Hsc70/ATPase was flowed over the chips (arrow/left) until maximal binding was reached (response units), then flow was continued without Hsc70/ATPase (arrow/right). For BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6), Hsc70 was injected at 0.0175, 0.035, 0.07, 0.14, and 0.28 μM.

Figure 14 shows BAG-family protein modulation of Hsc70 chaperone activity. (A) Protein refolding assay of chemically-denatured luciferase by Hsc70 plus DnaJ in the absence or presence of BAG and BAG-mutant proteins. (B) Concentration-dependent inhibition of Hsc70-mediated protein refolding by BAG-family proteins [BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6)] but not by BAG-mutant (BAG-1 (ΔC). (C) Hsc70/Hsp40-mediated refolding of heat-denatured luciferase was assayed in the presence of (black bars) or absence of (striped bars) of 1.8 μM Hip, with (lanes 3-10) or without (lanes 1,2) various BAG-family proteins (1.8μM) as indicated (mean ±SE; n=3). A control (CNTL) is shown (lane 1) in which Hsc70 was replaced with an equivalent amount of BSA.

Figure 15A shows an expanded cDNA sequence for human BAG-3 protein (SEQ ID NO:19).

Figure 15B shows the corresponding amino acid residues for the human BAG-3 protein (SEQ ID NO:20) of Figure 15A.

Figure 15C shows the expanded cDNA sequence (SEQ ID NO:19) aligned with the corresponding amino acid residues for human BAG-3 protein of Figure 15A (SEQ ID NO:20).

Figure 16A shows an expanded cDNA sequence for human BAG-4 protein (SEQ ID NO:21).

Figure 16B shows the corresponding amino acid residues for the human BAG-4 protein of Figure 16A (SEQ ID NO:22).

Figure 16C shows the expanded cDNA sequence (SEQ ID NO:21) aligned with the corresponding amino acid residues for human BAG-4 protein of Figure 16A (SEQ ID NO:22).

Figure 17A shows an expanded cDNA sequence for human BAG-5 protein (SEQ ID NO:23).

Figure 17B shows the corresponding amino acid residues for the human BAG-5 protein of Figure 17A (SEQ ID NO:24).

Figure 17C shows the expanded cDNA sequence (SEQ ID NO:23) aligned with the corresponding amino acid residues for human BAG-5 protein of Figure 17A (SEQ ID NO:24).

BNSDOCID: <WO__0014106A1_I_>

Figure 18 shows the topologies of the BAG-family proteins; human BAG proteins, BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), expanded BAG-3 (SEQ ID NO:20), expanded BAG-4 (SEQ ID NO:22), expanded BAG-5 (SEQ ID NO:24); *S.pombe* BAG-1A (SEQ ID NO:16)and BAG-1B (SEQ ID NO:18); and *C. elegans* BAG-1 (SEQ ID NO:12)and BAG-2 (SEQ ID NO:14). The relative positions of the BAG domains are shown in black, ubiquitin-like regions are represented in gray, WW domain are represented in strips. Nucleoplasmin-like nuclear localization sequence are also shown.

Definitions

The term "apoptosis", as used herein, refers to the process of programmed cell death, although not all programmed cell deaths occur through apoptosis, as used herein, "apoptosis" and "programmed cell death" are used interchangeably.

The term "tumor cell proliferation", as used herein refers to the ability of tumor cells to grow and thus expand a tumor mass.

The term "cell migration", as used herein refers to the role cell motility plays in the invasion and potentially metastasis by tumor cells.

The term "metastasis", as used herein refers to the spread of a disease process from one part of the body to another, as in the appearance of neoplasms in parts of the body remote from the site of the primary tumor; results in dissemination of tumor cells by the lymphatics or blood vessels or by direct extension through serious cavitites or subarachnoid or other spaces.

The term "steroid hormone receptor function", as used herein refers to physiological, cellular and molecular functioning of receptors sites that bind with steroid hormones.

The term "substantially purified", as used herein, refers to nucleic acid or amino acid sequence that are removed from their natural environment, isolated or separated, and are at least 60% free, preferably 75% free, and most preferably 90% free from other components with which they are naturally associated.

"Nucleic acid molecule" as used herein refers to an oligonucleotide, nucleotide, or polynucleotide, and fragments or portions thereof, and to DNA or RNA of genomic or synthetic origin which may be single or double stranded, and represent the sense or antisense strand.

"Hybridization", as used herein, refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The terms "complementary" or "complementarity", as used herein, refer to the natural binding of polynucleotides under permissive salt and temperature conditions by base-pairing. For example, the sequence "A-G-T binds to the complementary sequence "T-C-A".

The term "homology", as used herein, refers to a degree of complementarity. There may be partial homology or complete homology (i.e., identity). A partially complementary sequence is one that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid and is referred to using the functional term "substantially homologous." The inhibition of

BNSDOCID <WO 0014106A1 | >

hybridization of the completely complementary sequence to the target sequence may be examined using a hybridzation assay (Southern or northern blot, solution hybridization and the like) under conditions of low stringency. A substantially homologous sequence or probe will compete for and inhibit the binding (i.e., the hybridization) of a completely homologous sequence or probe to the target sequence under conditions of low stringency.

The term "antisense", as used herein, refers to nucleotide sequences which are commplementary to a specific DNA or RNA sequence. The term "antisense strand" is used in reference to a nucleic acid strand that is complementary to the "sense" strand. Antisense molecules may be produced by any method, including synthesis by ligating the gene(s) of interest in a reverse orientation to a viral promoter which permits the synthesis of a complementary strand. Once introduced into a cell, this transcribed strand combines with natural sequences produced by the cell to form duplexes. These duplexes then block either the further transcription or translation. In this manner, mutant phenotypes may be generated. The designation "negative" is sometimes used in reference to the antisense, and "positive" is sometimes used in reference to the sense strand.

"Amino acid sequence" as used herein refers to an oligopeptide, peptide, polypeptide, or protein sequence, and fragments or portions thereof, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited herein this term excludes an amino acid sequence of a naturally occurring protein. "Amino acid sequence", "polypeptide" or "protein" are not meant to limit the amino acid sequence to the complete, native amino acid sequence associated with the recited protein molecule.

The term "functional fragments" or "fragments", as used herein, with regard to a protein refers to portions of that protein that are capable of exhibiting or carrying out the activity exhibited by the protein as a whole. The portions may range in size from three amino acid residues to the entire amino acid sequence minus one amino acid. For example, a protein "comprising at least a functional fragment of the amino acid sequence of SEQ ID NO:1", encompasses the full-length of the protein of SEQ ID NO:1 and portions thereof.

A "derivative" of a BAG protein, as used herein, refers to an amino acid sequence that is alterd by one or more amino acids. The derivative may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties, e.g., substitution of an apolar amino acid with another apolar amino acid (such as replacement of leucine with isoleucine). The derivative may also have "nonconservative" changes, wherein a substituted amino acid has different but sufficiently similar structural or chemical properties that permits such a substitution without adversely effecting the desired biological activity, e.g., replacement of an amino acid with an uncharged polar R group with an amino acid with an apolar R group (such as replacement of glycine with tryptophan), or alternatively replacement of an amino acid with a charged R group with an amino acid with an uncharged Polar R group (such as replacement of lysine with asparagine).

BNSDOCID <WO 0014106A1 | >

Amino Acids - Apolar R Groups

Amino Acid	Radical	Abbreviations	
		3-Letter	1-Letter
alanine	methyl	ala	A
valine	2-propyl	aal	V
leucine	2-methylpropyl	leu	L
isoleucine	2-butyl	ile	I
proline	propyl* - cyclized	pro	P
phenylalanine	benzyl	phe	F
trytophan	3-indolylmethl	tyr	W
methionine	methylthioethyl	met	M

Amino Acids - Uncharged Polar R Groups

Amino Acid	Radical	Abbreviations	
		3-Letter	1-Letter
glycine	H	gly	G
serine	hydroxymethyl	ser	S
threonine	1-hydroxyethyl	thr	T
cysteine	thiolmethyl	cys	C
tyrosine	4-hydroxyphenylmethyl	tyr	Y
asparagine	aminocarbonylmethyl	asn	N
glutamine	aminocarbonylethyl	gln	Q

Amino Acids - Charged R Groups

Amino Acid	Radical	Abbreviations	
		3-Letter	1-Letter
aspartic acid	carboxymethyl	asp	D
glutamic acid	carboxyethyl	glu	E
lysine	4-aminobutyl	lys	K
arginine	3-guanylpropyl	arg	R
histidine	4-imidazoylmethyl	his	H

Similar minor modifications may also include amino acids deletions or insertions or both. Guidance in determining which amino acid residues may be modified as indicated above without abolishing the desired biological functionality may be determined using computer programs well known in the art, for example, DNASTAR software. In addition, the derivative may also result from chemical modifications to the encoded polypeptide, including but not limited to the following, replacement of hydrogen by an alkyl, acyl, or amino group; esterification of a carboxyl group with a suitable alkyl or aryl moiety; alkylation of a hydroxyl group to form an ether derivative. Further a derivative may also result from the substitution of a L-configuration amino acid with its corresponding D-configuration counterpart.

The term "mimetic", as used herein, refers to a molecule, the structure of which is developed from knowledge of the structure of a protein/polypeptide or portions thereof (such as BAG-1) and, as such, is able to effect some or all of the actions of BAG-1 protein.

"Peptide nucleic acid", as used herein, refers to a molecule which comprises an oligomer to which an amino acid residue, such as lysine, and an amino group have been added. These small molecules, also designated anti-gene agents, stop transcript elongation by binding to their complementary strand of nucleic acid (Nielsen, P.E. et al., *Anticancer Drug Des.* 8:53-63 (1993)).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a family of BAG-1 related proteins from humans [BAG-1L (SEQ ID NO:2), BAG-1S beginning at residue 116 of SEQ ID NO:2, BAG-2 (SEQ ID

BNSDOCID <WO 0014106A1 | >

NO:4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO: 8) and (SEQ ID NO:22) and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24)], the invertebrate C.*elegans* [BAG-1 (SEQ ID NO:12), BAG-2 (SEQ ID NO:14)] and the fission yeast S.*pombe* [BAG-1A (SEQ ID NO:16), BAG-1B (SEQ ID NO:18)], specifically the full length amino acid sequences comprising human BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), and BAG-2 (SEQ ID NO:4) *C. elegans* BAG-1 (SEQ ID NO:12), and BAG-2 (SEQ ID NO:14), and *S.pombe* BAG-1A (SEQ ID NO:16) and BAG-1B (SEQ ID NO:18); and partial sequences comprising human BAG-3 (SEQ ID NO: 6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22), and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24) and functional fragments thereof. In particular, the invention provides the amino acid sequences comprising human BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22), and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24) proteins.

Another aspect of the present invention provides the nucleic molecule and nucleotide sequences that encode the family of BAG-1 related proteins from humans [BAG-1 (SEQ ID NO:1), BAG-2 (SEQ ID NO:3), BAG-3 (SEQ ID NO:5) and (SEQ ID NO:19), BAG-4 (SEQ ID NO:7) and (SEQ ID NO:21) and BAG-5 (SEQ ID NO:9) and (SEQ ID NO:23)], the invertebrate C.*elegans* [BAG-1 (SEQ ID NO:11), BAG-2(SEQ ID NO:13)] and the fission yeast S.*pombe* [BAG-1A (SEQ ID NO:15), BAG-1B (SEQ ID NO:17)].

BAG-1L (SEQ ID NO:2) is a multifunctional protein that blocks apoptosis, promotes tumor cell metastasis, and contributes to factor-independent and p53-resistant cell growth. BAG-1L (SEQ ID NO:2) interacts with several types of proteins, including Bcl-2, some tyrosine kinase growth

factor receptors, steroid hormone receptors, and the p53-induced cell cycle regulator Siah-1A.

BAG-1 is a regulator of Hsc70/Hsp70 family molecular chaperones. A carboxyl-terminal domain in this protein binds tightly to the ATPase domains of Hsc70 and Hsp70 (K_D = 1 nM) (Zeiner, M., Gebauer, M., and Gehring, U., *EMBO J.* ***16:*** 5483-5490, (1997)). BAG-1 modulates the activity of these molecular chaperones, acting as an apparent functional antagonist of the Hsp70/Hsc70-associated protein Hip (3-5)(Höhfeld, J. and Jentsch, S., *EMBO J.* ***16:*** 6209-6216, (1997); Takayama, S., Bimston, D. N., Matsuzawa, S., Freeman, B. C., Aime-Sempe, C., Xie, Z., Morimoto, R. J., and Reed, J. C., *EMBO J.* ***16:*** 4887-96, (1997); Zeiner, M., Gebauer, M., and Gehring, U., *EMBO J.* ***16:*** 5483-5490, (1997)). In general, protein refolding is accomplished by Hsp70/Hsc70 through repeated cycles of target peptide binding and release, coupled to ATP hydrolysis (Ellis, R., *Curr Biol.* **7**: R531-R533, (1997)). BAG-1 appears to promote substrate release, whereas Hip stabilizes Hsp70/Hsc70 complex formation with target peptides (Höhfeld, J., Minami, Y., and Hartl, F.-U., *Cell.* **83**: 589-598, (1995)). Since each substrate interaction with Hsc70/Hsp70 is unique in terms of the optimal length of time the protein target should remain complexed with Hsc70/Hsp70 for achieving new conformations, the net effect of BAG-1 can be either enhancement or inhibition of the refolding reaction.

The 70kd heat shock family proteins (Hsp70/Hsc70) are essential to a variety of cellular processes and have been implicated in cancer, yet it is unclear how these proteins are regulated *in vivo*. A variety of co-chaperones have been identified which may target Hsp70/Hsc70 to different subcellular compartments or promote their

BNSDOCID <WO 0014106A1 I >

interactions with specific protein or protein complexes. BAG-1 appears to represent a novel Hsp70/Hsc70 regulator which differs functionally from all other mammalian co-chaperones identified to date, such as members of the DnaJ-, Hip-, Hop-, and cyclophilin-families of proteins.

Another aspect of the present invention provides the amino acid sequence of a binding domain of about 40 to 55 amino acids that bind the a Hsc70/Hsp70 ATPase domain. The BAG domain is situated near the C-terminus, and the ubiquitin-like domains are situated near the N-terminus.

The BAG family of proteins of the present invention contain a common conserved C-terminal domain (the "BAG" domain) that facilitates binding to the ATPase domain of Hsp70/Hsc70. The carboxyl-terminal domain of BAG-1 binds to the ATPase domain of Hsc70/Hsp70 and regulates its chaperone function by acting as a ADP-ATP exchange factor. Other domains of BAG-1 mediate interactions with proteins such as Bcl-2 and retinoic acid receptors (RARs), allowing BAG-1 to target Hsc70/Hsp70 to other proteins, presumably modulating their function by changing their conformations.

Human BAG-1 was previously shown to inhibit Hsc70/Hsp70 dependent refolding of denatured protein substrates *in vitro* (S. Takayama, et al., *EMBO J* **16**, 4887-96 (1997); M. Zeiner, M. Gebauer, U. Gehring, *EMBO J.* **16**, 5483-5490 (1997); and J. Höhfeld, S. Jentsch, *EMBO J.* **16**, 6209-6216 (1997)). In Example III, Part A the effects of recombinant human BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) were compared using *in vitro* protein refolding assays similar to those employed previously for assessing BAG-1. The study showed that addition of equimolar amounts of each of the recombinant proteins to Hsc70 resulted in significant inhibition of luciferase refolding, with BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) showing somewhat

greater inhibitor activity than BAG-1 (Figure 4A). In a separate luciferase folding study BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) once again displayed inhibition of luciferase refolding, however in this study varying amounts of BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) were added relative to Hsc70 which resulting in concentration-dependent inhibition of Hsc70 chaperone activity, i.e., luciferase folding (Example III Part A). Additional follow on studies using the same experimental protocols as the previous studies, as taught in Example IIA, have shown that BAG-4 (SEQ ID NO:22) also undergoes association with Hsc70/ATPase.

Yet another aspect of the present invention provides a nucleotide sequence having at least about 15 nucleotides and, generally, about 25 nucleotides, preferably about 35 nucleotides, more preferably about 45 nucleotides, and most preferably about 55 nucleotides that can hybridize or is complementary under relatively stringent conditions to a portion of the nucleic acid sequences shown in Figures 1-9 and Figures 15-17, in particular the BAG domain as shown in in Figure 1B, e.g., nucleotides 552-593 of human BAG-3, or nucleotides 167-221 of human BAG-4.

Yet another aspect of the present invention provides a compound of the formula,

$$R^N\text{-}R^1X^1R^2X^2R^3X^3R^4X^4R^5X^5R^6X^6R^7X^7X^8R^9X^9R^{10}X^{10}R^{11}X^{11}\text{-}R^C$$

wherein,

R^N is a group of 1 to 552 independently selected amino acids;

R^1 is a group of 3 independently selected amino acids;

BNSDOCID <WO 0014106A1 | >

X^1 is an amino acid with a charged or uncharged R group, such as aspartic acid, glutamic acid, asparagine, or glutamine;

R^2 is a group of 7 independently selected amino acids;

X^2 is an amino acid with a charged R group, such as glutamic acid;

R^3 is a group of 5 independently selected amino acids;

X^3 is an amino acid with an apolar R group, such as leucine, methionine, or isoleucine;

R^4 is a group of 3 independently selected amino acids;

X^4 is an amino acid with charged R group, such as aspartic acid or glutamine acid;

R^5 is a single independently selected amino acid;

X^5 is an amino acid with apolar or uncharged R group, such as leucine, valine, methionine, alanine or threonine;

R^6 is a group of 15 independently selected amino acids;

X^6 is an amino acid with a charged or uncharged R group, such as arginine, lysine, glutamine or aspartic acid;

R^7 is a group of 2 independently selected amino acids;

X^7 is an amino acid with a charged R group, such as arginine;

X^8 is an amino acid with a charged R group, such as arginine or lysine;

R^9 is a group of 2 independently selected amino acids;

X^9 is an amino acid with an apolar R group, such as valine;

R^{10} is a group of 3 independently selected amino acids;

BNSDOCID <WO__0014106A1 >

X^{10} is an amino acid with an uncharged R group, such as glutamine;

R^{11} is a group of 2 independently selected amino acids;

X^{11} is an amino acid with an apolar R group, such as leucine; and

R^{C} is a group of 1 to 100 independently selected amino acids.

A nucleotide sequence of at least about 15 nucleotides and, generally, about 25 nucleotides, preferably about 35 nucleotides, more preferably about 45 nucleotides, and most preferably about 55 nucleotides can be useful, for example, as a primer for the polymerase chain reaction (PCR) or other similar reaction mediated by a polymerase such as a DNA or RNA polymerase (see PCR Protocols: A guide to methods and applications, ed. Innis et al. (Academic Press, Inc., 1990), which is incorporated herein by reference; see, for example, pages 40-41). In addition, such a nucleotide sequence of the invention can be useful as a probe in a hybridization reaction such as Southern or northern blot analysis or in a binding assay such as a gel shift assay.

A nucleotide sequence of the invention can be particularly useful as an antisense molecule, which can be DNA or RNA and can be targeted to all or a portion of the 5'-untranslated region or of the 5'-translated region of a bag-1 nucleic acid sequence in a cell. For example, an antisense molecule can be directed to at least a portion of the sequence shown as the BAG domain in Figure 1A, e.g., nucleotides 272-319 of human BAG-1L (SEQ ID NO:1), or nucleotides 79-147 of human BAG-5 (SEQ ID NO:9). Since the 5'-region of a nucleic acid contains elements involved in the control of expression of an encoded protein, an antisense molecule directed to the 5'-region of a nucleic

BNSDOCID: <WO 0014106A1 I >

acid molecule can affect the levels of protein expressed in a cell.

A nucleotide sequence of the invention also can be useful as a probe to identify a genetic defect due a mutation of a gene encoding a BAG protein in a cell. Such a genetic defect can lead to aberrant expression of a BAG protein in the cell or to expression of an aberrant BAG protein, which does not properly associate with a Bcl-2-related protein or Hsc70/Hsp70 protein in the cell. As a result, a genetic defect in a gene encoding, for example, human BAG-1 can result in a pathology characterized by increased or decreased levels in protein folding.

Further a nucleotide compound or composition as taught in the present invention can be synthesized using routine methods or can be purchased from a commercial source. In addition, a population of such nucleotide sequences can be prepared by restriction endonuclease or mild DNAse digestion of a nucleic acid molecule that contains nucleotides as shown in the nucleotide sequences shown in Figures 1-9 and Figures 15-17 that encodes the amino acids sequences also shown in Figures 1-9 and Figures 15-17. Methods for preparing and using such nucleotide sequences, for example, as hybridization probes to screen a library for homologous nucleic acid molecules are well known in the art (see, for example, Sambrook et al., *Molecular Cloning: A laboratory manual* (Cold Spring Harbor Laboratory Press 1989); Ausubel et al., *Current Protocols in Molecular Biology* (Green Publ., NY 1989), each of which is incorporated herein by reference).

A particular nucleotide sequence can be designed based, for example, on a comparison of the nucleic acid molecules encoding any one of the BAG family proteins, as shown in Figures 1-9 and Figures 15-17, with another in the family. Such a comparison allows, for example, the

preparation of a nucleotide sequence that will hybridize to a conserved region present in both nucleic acid molecules, thus providing a means to identify homologous nucleic acid molecules present in other cell types or other organisms. In addition, such a comparison allows the preparation of a nucleotide sequence that will hybridize to a unique region of any of the BAG family nucleotide sequences, such as those corresponding to the BAG domain, thus allowing identification of other proteins sharing this motif. In this regard, it is recognized that, while the human BAG-3 proteins shown as Figures 3 and 20, and human BAG-5 proteins shown as Figures 5 and 24, are only partial sequences, a variant human BAG-3 or BAG-5 produced, for example, by alternative splicing can exist and can be identified using an appropriately designed nucleotide sequence of the invention as a probe. Such useful probes readily can be identified by inspection of the sequences shown in the disclosed Figures by a comparison of the encoding nucleotide sequences.

If desired, a nucleotide sequence of the invention can incorporate a detectable moiety such as a radiolabel, a fluorochrome, a ferromagnetic substance, a luminescent tag or a detectable binding agent such as biotin. These and other detectable moieties and methods of incorporating such moieties into a nucleotide sequence are well known in the art and are commercially available. A population of labelled nucleotide sequences can be prepared, for example, by nick translation of a nucleic acid molecule of the invention (Sambrook et al., *supra*, 1989; Ausubel et al., *supra*, 1989).

One skilled in the art would know that a method involving hybridization of a nucleotide sequence of the invention can require that hybridization be performed under relatively stringent conditions such that nonspecific background hybridization is minimized. Such hybridization

conditions can be determined empirically or can be estimated based, for example, on the relative GC content of a sequence and the number of mismatches, if known, between the probe and the target sequence (see, for example, Sambrook et al., *supra*, 1989).

The invention further provides antibodies specific for human BAG family protein. As used herein, the term "antibody" includes polyclonal and monoclonal antibodies, as well as polypeptide fragments of antibodies that retain a specific binding activity for human BAG-1 of at least about 1×10^5 M^{-1}. One skilled in the art would know that anti-BAG-1 antibody fragments such as Fab, $F(ab')_2$ and Fv fragments can retain specific binding activity for human BAG-1 (beginning at residue 116 of SEQ ID NO:2) and, thus, are included within the definition of an antibody. In addition, the term "antibody" as used herein includes naturally occurring antibodies as well as non-naturally occurring antibodies and fragments that retain binding activity such as chimeric antibodies or humanized antibodies. Such non-naturally occurring antibodies can be constructed using solid phase peptide synthesis, can be produced recombinantly or can be obtained, for example, by screening combinatorial libraries consisting of variable heavy chains and variable light chains as described by Huse et al., *Science* **246**:1275-1281 (1989), which is incorporated herein by reference.

One skilled in the art would know that purified BAG family protein, which can be prepared from natural sources or synthesized chemically or produced recombinantly, or portions of a BAG family protein, including a portion of human BAG family protein such as a synthetic peptide as described above, can be used as an immunogen. Such peptides useful for raising an antibody include, for example, peptide portions of the N-terminal 85 amino acids or the BAG domain of any of the human BAG

BNSDOCID <WO 0014106A1 I_>

proteins (see Figure 1B). A particularly advantageous use of such a protein is for the immunostaining, wherein the methods provides a process to contrast the immunostaining of BAG-family proteins in carcinoma cells with adjacent non-neoplastic prostatic epithelial and basal cells which are generally present in the same tissue sections. These results would be correlated with a Gleason grade to determine whether any of the BAG-family proteins tend to be expressed at higher or lower levels in histologically advanced tumors. From this process a determination can be made as to degree at which the disease is progressing in a given patient, i.e., a prognosis can be made.

Non-immunogenic fragments or synthetic peptides of BAG proteins can be made immunogenic by coupling the hapten to a carrier molecule such bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH), as described in Example IV, below. In addition, various other carrier molecules and methods for coupling a hapten to a carrier molecule are well known in the art and described, for example, by Harlow and Lane, *Antibodies: A laboratory manual* (Cold Spring Harbor Laboratory Press, 1988), which is incorporated herein by reference.

EXAMPLES

The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

BNSDOCID <WO 0014106A1 >

EXAMPLE I

Isolation and Characterization of BAG-family cDNA Sequences

This example describes methods for isolating and characterizing of BAG-family cDNA sequences from human, nematode and yeast.

A. Cloning of human BAG cDNA sequences

Yeast two-hybrid library screening of a human Jurkat cell cDNA library was performed as described by Takayama et al., EMBO J., 16:4887-96 (1997); Matsuzawa et al., EMBO J., 17:2736-2747 (1998), which are incorporated herein by reference) using EGY48 strain yeast transformed with pGilda-Hsc70/ATPase (67-377 amino acids) and the *lacZ* reporter plasmid pSH18-34. Of the resulting ~5 x 10^6 transformants, 112 Leu$^-$ colonies were obtained after 1 week incubation at 30°C. Assay of β-galactosidase (β-gal) activity of these colonies resulted in 96 clones. Mating tests were then performed using RFY206 yeast strain transformed with pGilda, pGilda mBAG-1 (1-219), or pGilda Hsc70/ATPase. Of these, 66 displayed specific interactions with Hsc70/ATPase. The pJG4-5 cDNAs were recovered using KC8 *E. coli* strain which is auxotrophic for tryptophan (Trp). DNA sequencing revealed 3 partially overlapping human BAG-1, 4 identical and one overlapping cDNAs encoding BAG-2, and 2 partially overlapping BAG-3 clones.

Using the above described yeast two-hybrid screen with the ATPase domain of Hsc70 as "bait", several human cDNAs were cloned which encode portions of BAG-1 or of two other BAG-1-like proteins which are termed BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6). The longest of the cDNAs for BAG-2 (SEQ ID NO:3) and BAG-3 (SEQ ID NO:5) contained open reading frames (ORFs) of 207 and 162 amino acids, respectively, followed by stop codons. All BAG-1 (SEQ ID

BNSDOCID <WO__0014106A1_>

NO:1), BAG-2 (SEQ ID NO:3) and BAG-3 (SEQ ID NO:5) cDNAs obtained by two-hybrid library screening with Hsc70/ATPase contained a conserved domain of about 40-50 amino acids which are termed the "BAG" domain and are shown in Figure 10. These results demonstrate that a family of BAG-1-related proteins all contain a conserved ~45 amino acid region near their C-terminus that binds Hsc70/Hsp70.

B. Identification of additional BAG-family proteins

A search of the translated Genbank database using the bBLAST and FASTA search programs also identified human ESTs that provided sequences for further investigation of BAG-family proteins. The putative BAG-4 (SEQ ID NO:8) and BAG-5 (SEQ ID NO:10) proteins contain BAG-domains that share the greatest sequence similarity with the BAG-domain of BAG-3 (SEQ ID NO:6). These were designated BAG-4 (Accession number AA693697, N74588) and BAG-5 (Accession number AA456862, N34101). BAG-4 has 62% identity and ~81% similarity to BAG-3, and BAG-5 has 51% identity and ~75% similarity to BAG-3.

Additional BAG-family orthologues or homologues were also identified using computer-based searches and resulted in BAG-family homologue in the nematode *C. elegans* and the fission yeast *S. pombe*. The *C. elegans* genome encodes two apparent BAG-family proteins, which are most similar in their overall sequences to the human BAG-1 (Afo39713, gi:2773211) (SEQ ID NO:12) and BAG-2 (SEQ ID NO:14) (Afo68719, gi:3168927). The *S. pombe* contains two BAG-family proteins that share the greatest overall sequence similarity with human BAG-1 (Alo23S54,gi/3133105 and Alo23634, gi/3150250). The human and *C. elegans* BAG-1 proteins as well as *S. pombe* BAG-1A all have ubiquitin-like domains near their N-termini (see Figure 10A) of unknown function.

BNSDOCID <WO 0014106A1 | >

The overall predicted amino acid sequences of the *C. elegans* BAG-1 (SEQ ID NO:12) and *S. pombe* BAG-1A (SEQ ID NO:16) proteins are ~18% identical (~61% similar) and ~17% identical (~64% similar), respectively, to human BAG-1, implying origin from a common ancestral gene. The *C. elegans* BAG-1 protein (SEQ ID NO:12), however, contains a 5 to 7 amino acid insert in its BAG-domain as compared to the human, murine, and yeast BAG-1 homologues (see Figure 10B), and is more similar to BAG-2 (SEQ ID NO:4) in regard to its BAG-domain. *C. elegans* and human BAG-2 also may be derived from a common ancestor as the C-terminal 225 amino acid region which encompasses both the BAG domain and upstream region of both *C. elegans* and human BAG-2 share ~34% amino acid sequence identity and ~70% similarity. The human BAG-2 protein (SEQ ID NO:4), however, contains a 9 amino acid insert in its BAG-domain compared to it *C.elegans* counterpart (see Figure 10B). Evolutionary-tree prediction algorithms suggest that human and *C. elegans* BAG-2 represent a distinct branch of the BAG-family that is more evolutionarily distant from the other BAG-family proteins. None of the predicted BAG-family proteins contain recognizable regions analogous to those found in other Hsc70 regulatory proteins, such as the J-domains and G/F-domains of DnaJ family proteins and the Tetratricopeptide Repeat (TR) domains of Hip/Hop family proteins.

C. Yeast two-hybrid assay of BAG binding to Hsc70/ATPase

The longest of the cDNAs obtained for the BAG-2 and BAG-3 proteins were expressed with N-terminal transactivation (TA) domains in yeast and tested by yeast two-hybrid assay for interactions with fusion proteins consisting of Hsp70/ATPase or a variety of unrelated proteins (Fas, Siah, Fadd) containing N-terminal LexA DNA-binding domains. TA-BAG-2 and TA-BAG-3 demonstrated

positive interactions with LexA-Hsc70/ATPase, resulting in transactivation of a *lacZ* reporter gene that was under the control of LexA operators (Figure 11A). No interactions with LexA-Fas (cytosolic domain), LexA-Siah, LexA-Fadd, or LexA were detected (see Figure 11A) demonstrating that the BAG-2 and BAG-3 proteins interact specifically with Hsc70/ATPase. Specific two-hybrid interactions between Hsc70/ATPase and either BAG-2 or BAG-3 were also observed when BAG-2 and BAG-3 were expressed as LexA DNA-binding domain fusion proteins and Hsc70/ATPase was fused with a TA domain (see Figure 11A; right panel). These results demonstrate that similarly to BAG-1, BAG-2 and BAG-3 specifically interact with Hsc70/ATPase.

In order to determine whether the BAG proteins are capable of forming heterodimers, coexpression of BAG-2 and BAG-3 in the yeast two-hybrid assay was also performed. Coexpression of BAG-2 and BAG-3 failed to show interaction with BAG-1 or a deletion mutant of BAG-1 (ΔC) which is missing part of its C-terminal domain required for Hsp70/Hsc70 binding suggest that these proteins do not form heterdimers.

D. Isolation and characterization of the complete open reading frame sequences of BAG-2 and BAG-3

In order to deduce the complete ORFs of BAG-2 and BAG-3, a λ-phage cDNA library was screened as follows, using hybridization probes derived from the two-hybrid screening. A human jurkat T-cell λ-ZapII library cDNA library (Stratagene) was screened by hybridization using ^{32}P-labeled purified insert DNA from the longest of the human BAG-2 (clone #11) and human BAG-3 (clone #28) cDNA clones. From about one million clones screened, 38 BAG-2 and 23 BAG-3 clones were identified, cloned, and their cDNA inserts recovered as pSKII plasmids using a helper phage method (Stratagene). DNA sequencing of λ-phage derived

human BAG-2 cDNA clones revealed an ORF encoding a predicted 211 amino acid protein, preceded by an in-frame stop codon. The longest human BAG-3 λ-phage cDNA clone contains a continuous ORF of 682 amino acids followed by a stop codon, but without an identifiable start codon (see Figure 10A).

Although BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) all contain a homologous BAG domain near their C-terminus, the N-terminal regions of these proteins are dissimilar. Using a combination of search tools (Prosite Search: PP search, using the Prosite pattern database, BCM Search Launcher, Baylor College of Medicine, and Blocks Search), it was determined that the BAG-2 N-terminal region contains potential kinase phosphorylation sites but otherwise shares no apparent similarity with other proteins or known functional domains.

In contrast, the predicted N-terminal region BAG-3 contains a WW domain as shown in Figure 10A. WW domains have been identified in a wide variety of signaling proteins, including a Yes kinase adaptor protein (YAP), the Na^+-channel regulator Nedd4, formin-binding proteins, dystrophin, and the peptidyl prolyl cis-trans-isomerase Pin-1. These roughly 40 amino acid domains mediate protein interactions and bind the preferred peptide ligand sequence xPPxY (Sudol., TIBS, 21: 161-163, 1996, which is incorporated herein by reference).

EXAMPLE II

In vitro Association of BAG proteins and Hsc70/ATPase

This example demonstrates that BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) bind Hsc70/ATPase in various *in vitro* assays.

A. Solution binding assay of BAG-2 and BAG-3 to Hsc70/ATPase

Association of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) with Hsc70/ATPase was determine by an *in vitro* protein binding assay where Hsc70/ATPase or BAG-family proteins were expressed in bacteria as Glutathione S-Transferase (GST) fusion proteins. Purified cDNA sequences encoding residues 5 to 211 of human BAG-2 (clone #11) and the C-terminal 135 amino acids of human BAG-3 (clone #28) (see Figure 10A) were subcloned into the EcoRI/Xho I sites of pGEX4T-1 prokaryotic expression plasmid (Pharmacia; Piscataway, NJ). These plasmids as well as pGEX4T-1-BAG-1, pGEX-4T-1-BAG-1 (ΔC), and pGEX-4T-1-XL which have been described previously (Takayama et al., *supra* (1997); Xie et al., Biochemistry, 37:6410-6418, (1998), which are incorporated herein by reference), were expressed in XL-1 blue strain *E. Coli* (Stratagene, Inc., La Jolla, CA). Briefly, a single colony was inoculated into 1L of LB media containing 50 μg/ml ampicillin and grown at 37°C overnight. The culture was then diluted by half with fresh LB/ampicillin and cooled to room temperature for 1 hr, before inducing with 0.4mM IPTG for 6 h at 25°C.

Cells were recovered and incubated with 0.5 mg/ml lysozyme in 50 mM Tris (pH 8.0), 150 mM NaCl, 1% Tween-20, 0.1% 2-mercaptoethanol, 5 mM EDTA, 1 mM PMSF and a mixture

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of other protease inhibitors obtained from Boehringer Mannheim (1697498) at room temperature for 0.5 h, followed by sonication. Cellular debris were pelleted by centrifugation at 27,500g for 10 min and the resulting supernatants were incubated with 30 ml of glutathionine-Sepharose (Pharmacia) at 4°C overnight. The resin was then washed with 20 mM Tris (pH 8.0), 150 mM NaCl, 0.1% Tween-20, and 0.1% 2-mercaptoethanol until the OD 280nm reached <0.01. For removal of GST, the resin with immobilized GST-fusion protein was incubated with 10U of thrombin (Boehringer, Inc.) at 4°C in 20 mM Tris (pH 8.0), 150 mM NaCl, 0.1% Tween-20, 0.1% 2-Mercaptoethanol, and 2.5 mM CaCl2 overnight. Released proteins were then purified on Mono Q (HR10/10, Pharmacia) by FPLC using a linear gradient of 0.5M NaCl at pH 8.0 and dialyzed into chaperone assay buffer.

The ability of BAG-2 (SEQ ID NO:4) or BAG-3 (SEQ ID NO:6) to bind Hsc70/ATPase in solution was then examined. GST control or GST-BAG proteins were immobilized on glutathione-Sepharose and tested for binding to 35S-labeled *in vitro* translated (IVT) proteins. Immunoprecipitation and *in vitro* GST-protein binding assays were performed as described by Takayama et al., *supra* (1997), using pCI-Neo flag or pcDNA3-HA into which human Bag-2 (clone #11) or human BAG-3 (clone #28) had been subcloned for *in vitro* translation of 35S-L-methionine labeled proteins or expression in 293T cells. As shown in Figure 11B, ^{35}S-Hsc70/ATPase bound *in vitro* to GST-BAG-1, GST-BAG-2, and GST-BAG-3 but not to GST-BAG-1(ΔC) or several other control proteins. BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) also exhibited little or no binding to themselves or to each other, demonstrating that these proteins do not strongly homo- or hetero-dimerize or oligomerize. It should be noted, however, that BAG-2 (SEQ

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ID NO:4) displayed weak interactions with itself in binding assays and produced a positive result in yeast two-hybrid experiments, demonstrating that it can have the ability to self-associate.

B. Binding of BAG proteins to Hsc70 *in vivo*

The ability of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins to interact in cells with Hsc70 was tested by expressing these proteins with N-terminal Flag epitope tags in 293T human epithelial cells using co-immunoprecipitation assays as described previously (Takayama et al., *supra* (1997)). cDNAs encoding the λ-phage cloned regions of BAG-2 and BAG-3 were subcloned in-frame into pcDNA3-Flag. Anti-Flag immune complexes prepared from 293T cells after transfection with plasmids encoding Flag-BAG-1, Flag-BAG-2, or Flag-BAG-3 were analyzed by SDS-PAGE/immunoblot assay. As shown in Figure 10C, antiserum specific to Hsc70 detected the presence of BAG proteins associated with Hsc70, whereas control immune-complexes prepared with IgG1 as well as anti-Flag immune complexes prepared from cells transfected with Flag-tagged control proteins, Daxx and Apaf-1, did not contain Hsc70 associated protein. These results further demonstrate that BAG-family proteins specifically bind to Hsc70.

C. BIAcore assay of BAG protein binding to the ATPase domain of Hsc70

BAG-1 (beginning at residue 116 of SEQ ID NO:2) is known to bind tightly to the ATPase domain of Hsc70 (Stuart et al., J. Biol. Chem., In Press (1998)). BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins were therefore, examined for their ability to bind to Hsc70/ATPase. The affinity and binding kinetics of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) to Hsc70/ATPase was also compared to that of BAG-1 (beginning at residue 116 of

SEQ ID NO:2) for Hsc70/ATPase, using a surface plasmon resonance technique (BIAcore) which has been described previously (Stuart et al., *supra*, (1998) which is incorporated herein by reference).

BAG-family proteins were produced in bacteria and purified to near homogeneity as shown in Figure 12A and described above in Example I. The purified BAG-1 (beginning at residue 116 of SEQ ID NO:2), -2 (SEQ ID NO:4), and -3 (SEQ ID NO:6) proteins were then immobilized on biosensor chips and tested for their interactions with Hsc70 in the soluble phase. Kinetic measurements were performed using a BIAcore-II instrument with CM5 sensor chip and Amine Coupling Kit (Pharmacia Biosensor AB, Sweden). Briefly, for immobilization of proteins, the sensor chip was equilibrated with HK buffer (10 mM Hepes (pH 7.4), 150 mM KCL) at 5μl/min, then activated by injecting 17 μl of 0.2M N-ethyl-N'-(3-diethylaminopropyl)-carbodiimide and 0.05M N-hydroxysuccinimide (NHS/EDC) followed by 35 μl of the protein of interest, in 10 mM acetate, pH 3.5-4.5. Excess NHS-ester on the surface was deactivated with 17 μl 1M ethanolamine-HCL (pH8.5). After immobilization, 5μl of regeneration buffer (50 mM phosphate (pH 6.8) and 4M GuHCl) was injected. For binding assays, Hsp70 (Sigma, H8778) was dissolved in HK buffer, and injected at 10 μl/min across the prepared surface at various concentrations. The surface was regenerated after each injection with 5 μl of regeneration buffer. The rate constants K_{ass} and K_{diss} were generated with BIAevaluation softward 3.01 (Pharmacia Biosensor AB). Addition of Hsc70 to chips containing BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4) or BAG-3 (SEQ ID NO:6) resulted in concentration-dependent binding, as reflected by an increase in the Response Units (RU) measured at the chip surface (shown in Figure 3B). In contrast, Hsc70 failed to display interactions in BIAcore assays with a variety of control proteins as well as a mutant of BAG-1

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lacking a C-terminal portion of the BAG domain which is required for Hsc70-binding (Figure 3B). Furthermore, flowing of various control proteins such as GST, BSA and Bcl-XL over the BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) chips resulted in negligible interaction. These results further demonstrate the specificity with which BAG-family proteins interact with and bind to Hsc70.

The rates of Hsc70 binding to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) proteins were similar, following pseudo first-order kinetics with estimated association rate constants (K_a) of 2.1, 2.1 and 2.4 x 10^5 M^{-1} sec^{-1}, respectively. After allowing binding of Hsc70 to immobilized BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) to reach plateau levels, the chaperone was removed from the flow solution and the dissociation rate was monitored. BAG-1 (beginning at residue 116 at SEQ ID NO:2) and BAG-2 (SEQ ID NO:4) exhibited similar dissociation rates, with relatively slow loss of Hsc70 from the chip surface, resulting in estimated dissociation rate constants (K_d) of 3.0 and 5.0 x 10^{-4} sec^{-1}, respectively (see Figure 3B). In contrast, Hsc70 dissociated more rapidly from biosensor chips containing BAG-3 (see Figure 3B), yielding an estimated K_d of 1.7 x 10^{-3} sec^{-1}. From the kinetic data, the apparent affinities ($K_D = K_d/K_a$) were calculated for binding of Hsc70 to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) and were estimated to equal about K_D= 1.4nM, K_D=2.4nM, and K_D=7.4nM, respectively. These results demonstrate that the interactions of BAG-family proteins with Hsc70 occur with apparent affinities sufficient for physiological relevance.

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EXAMPLE III

BAG-family proteins inhibit Hsp70/Hsc70-dependent protein folding

This example demonstrates that BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins inhibit Hsp70/Hsc70-dependent refolding of denatured proteins similarly to a BAG-1 (beginning at residue 116 of SEQ ID NO:2) protein.

The effects of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) protein on Hsp70/Hsc70-dependent protein refolding was determined using *in vitro* protein refolding assays similar to those described previously by Takayama et al., *supra*, 1998: Terada et al., J Cell Biol., 139:1089-1095, 1997, which are incorporated herein by reference. Briefly, luciferase (20μM) was denatured in 25 mM Hepes-KOH, pH 7.2, 50 mM potassium acetate, 5 mM DTT, 6M guanidine hydrochloride at ~25°C for 1 h. Denatured luciferase was diluted 1:40 into 25 mM Hepes-KOH, pH 7.2, 50 mM potassium acetate, 5 mM DTT. Hsc70 (1.8 μM), DnaJ (StressGen, Inc.) (0.9μM), and various purified recombinant proteins as indicated were added to refolding buffer (30 mM Hepes-KOH, pH 7.6, 120 mM potassium acetate, 3mM magnesium acetate, 2 mM DTT, 2.5 mM ATP) with 0.2 volume of diluted denatured luciferase to a final concentration of 0.1 μM. Luciferase activity was measured after 1.5 hr incubation at 35°C.

The combination of Hsc70 and DnaJ resulted in ATP-dependent refolding of chemically denatured firefly luciferase, with function of over half the denatured enzyme restored in a 90 minute reaction, as monitored by a chemiluminescence assay. In contrast, neither Hsc70 nor DnaJ alone were able to induce substantial refolding of denatured luciferase. Furthermore, little spontaneous

restoration of luciferase activity was observed with control proteins, BSA, GST or Bcl-XL (see Figure 4A).

Addition of recombinant purified BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) to the above assays in amounts equimolar to Hsc70 (1.8 μM) resulted in striking inhibition of luciferase refolding. BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) displayed somewhat greater inhibitory activity than BAG-1 (beginning at residue 116 of SEQ ID NO:2) as shown in Figure 4A. In contrast, the BAG-1 (ΔC) protein, which fails to bind Hsc70 as well as several other control proteins, had no effect on luciferase refolding.

In an additional refolding assay, described previously by Minami et al., J Biol. Chem. 271:19617-24, 1996), purified Hsc70 and human DnaJ homolog Hdj-1 (Hsp 40) were used with additional cofactors provided in reticulocyte lysates (5% v:v) to produce a system capable of refolding denatured luciferase. Briefly, additional cofactors included, recombinant Luciferase (Promega: QuantiLum TM), that had been heat denatured at 42°C for 10 min, 1.8 μM Hsc70 (Sigma; purified from bovine brain), 0.9 μM Hsp40, and various recombinant purified proteins. Luciferase activity was measured (Promega luciferase assay kit) using a luminometer (EG&G Berthold, MicroLumat luminometer, Model #LB96P). All results were normalized relative to non-denatured luciferase that had been subjected to the same conditions. Control reactions lacking ATP, Hsc70, or Hsp40 resulted in negligible luciferase refolding.

Various amounts of purified BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6), relative to amounts of Hsc70 were used in the above-described protein refolding assay. Addition of BAG-family proteins resulted in a concentration-dependent

inhibition of Hsc70 chaperone activity. Furthermore, the BAG-2 (SEQ ID NO:4)and BAG-3 (SEQ ID NO:6) inhibition of Hsc70 chaperone activity was demonstrated to be as potent as that observed for BAG-1 (beginning at residue 116 of SEQ ID NO:2). In contrast, the BAG-1 (ΔC) mutant as well as other control proteins did not suppress Hsc70-mediated refolding of denatured luciferase. These results indicate that BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) can inhibit Hsc70/Hsp70 dependent protein refolding activity to the same extent as BAG-1 (beginning at residue 116 of SEQ ID NO:2).

B. BAG competes with Hip for binding to Hsc70.

It is known that BAG-1 competes with Hip for binding to Hsc70, with these proteins exerting opposite effects on Hsc70-mediated protein refolding (Hohfeld, J., and Jentsch, S., *Embo J.*, 16:6209-6216, 1997, which is incorporated herein by reference). In order to determine whether BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) also compete with Hip for binding to Hsc70, refolding assays were performed as described above in the presence of Hip protein.

Hip was purified as His_6-protein. The fusion protein was induced from pET28-Hip (V. Prapapanich et al., *Mol Cell Biol.*, 18:944-952, 1998, which is incorporated herein by reference) with 0.1 mM IPTG at 25°C for 6h in BL21 cells. Cells from 1L of culture were resuspended into 50 ml of 50 mM Phosphate buffer (pH 6.8), 150 mM NaCl, and 1% (v/v) Tween-20 and then incubated with 0.5 mg/ml lysozyme at 25°C for 0.5h, followed by sonication. After centrifugation at 27,500g for 10 min, the resulting supernatant was mixed with 15 ml nickel resin (Qiagen, Inc.) at 4°C for 3 h with 25 mM imidazol. The resin was then washed with 50 mM phosphate buffer (pH 6.8), 25 mM imidazol, 150 mM NaCl and 0.1% Tween-20 until the OD280nm

BNSDOCID <WO 0014106A1 >

reached a value of <0.01. His_6-Hip protein was eluted with 250 mM imidazol in washing buffer (Qiagene, Inc.) and purified on Mono Q (HR10/10 Pharmacia) by FPLC using a linear gradient of 0.5M NaCl at pH 8.0, followed by dialysis in chaperone assay buffer.

In the refolding assay reactions, addition of purified Hip at equimolar concentrations relative to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) (1.8 μM) completely negated the inhibitory effects of the BAG-family proteins on refolding of denatured luciferase (see Figure 4C). These results demonstrate that the suppression of Hsc70 chaperone activity by BAG-family proteins is reversible, and that Hip antagonizes the effects of not only BAG-1 (beginning at residue 116 of SEQ ID NO:2), but also of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6).

In summary, these results demonstrate that BAG-family proteins all contain a conserved BAG domain near their C-terminus that binds Hsc70/Hsp70, and that human BAG-family proteins can bind with high affinity to the ATPase domain of Hsc70 and inhibit its chaperone activity through a Hip-repressable mechanism.

EXAMPLE IV

EXPANDED NUCLEIC ACID AND AMINO ACID SEQUENCES FOR HUMAN BAG-3, BAG-4 AND BAG-5

Following the procedures disclosed herein, the nucleic acid and amino acids sequences to human BAG-3, BAG-4 and BAG-5 were further expanded. The expanded sequences for BAG-3, BAG-4 and BAG-5 are shown in Figures 15, 16 and 17, respectively, with their respective sequence identification numbers, "SEQ ID NO"s.

BNSDOCID <WO 0014106A1 >

We claim:

1. A compound of the formula,

$$R^N\text{-}R^1X^1R^2X^2R^3X^3R^4X^4R^5X^5R^6X^6R^7X^7X^8R^9X^9R^{10}X^{10}R^{11}X^{11}\text{-}R^C$$

wherein,

R^N is a group of about 1 to 552 independently selected amino acids;

R^1 is a group of 3 independently selected amino acids;

X^1 is an amino acid with a charged or uncharged R group;

R^2 is a group of 7 independently selected amino acids;

X^2 is an amino acid with a charged R group;

R^3 is a group of 5 independently selected amino acids;

X^3 is an amino acid with an apolar R group;

R^4 is a group of 3 independently selected amino acids;

X^4 is an amino acid with charged R group;

R^5 is a single independently selected amino acid;

X^5 is an amino acid with apolar or uncharged R group;

R^6 is a group of 15 independently selected amino acids;

X^6 is an amino acid with a charged or uncharged R group;

R^7 is a group of 2 independently selected amino acids;

X^7 is an amino acid with a charged R group;

X^8 is an amino acid with a charged R group;

R^9 is a group of 2 independently selected amino acids;

X^9 is an amino acid with an apolar R group;

BNSDOCID <WO__0014106A1 !_>

R^{10} is a group of 3 independently selected amino acids;

X^{10} is an amino acid with an uncharged R group;

R^{11} is a group of 2 independently selected amino acids;

X^{11} is an amino acid with an apolar R group; and

R^{C} is a group of about 1 to 100 independently selected amino acids.

2. A substantially purified nucleic acid molecule having a nucleotide sequence corresponding to or complementary to at least 20 nucleotides from a nucleotide sequence selected from the group consisting of (SEQ ID NO:1), (SEQ ID NO:3), (SEQ ID NO:5), (SEQ ID NO:7), (SEQ ID NO:9), (SEQ ID NO:19), (SEQ ID NO:21) and (SEQ ID NO:23).

3. The nucleic acid of claim 2 having a nucleotide sequence corresponding to or complementary to a nucleotide sequence that encodes a functionally active BAG family protein selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24).

4. The nucleic acid of claim 3 selected from the group consisting of (SEQ ID NO:1), (SEQ ID NO:3), (SEQ ID NO:5), (SEQ ID NO:7), (SEQ ID NO:9), (SEQ ID NO:19), (SEQ ID NO:21) and (SEQ ID NO:23).

5. The nucleic acid of claim 3 complementary to a nucleotide sequence that encodes a functionally active BAG protein selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24).

6. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:3).

BNSDOCID <WO 0014106A1 >

7. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:5).

8. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:7).

9. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:9).

10. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:19).

11. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:21).

12. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:23).

13. A substantially purified BAG family protein encoded by the nucleic acid molecule of claim 1.

14. A substantially purified BAG family protein comprising of the amino acid sequence selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24) or a fragment, a derivative or a mimetic thereof.

15. A substantially purified protein corresponding to the amino acid sequence of 157 to 204 of (SEQ ID NO:2).

16. A substantially purified protein corresponding to the amino acid sequence of 272 to 319 of (SEQ ID NO:2).

17. A substantially purified protein corresponding to the amino acid sequence of 164 to 211 of (SEQ ID NO:4).

18. A substantially purified protein corresponding to the amino acid sequence of 418 to 510 of (SEQ ID NO:20).

19. A substantially purified protein corresponding to the amino acid sequence of 378 to 457 of (SEQ ID NO:22).

20. A substantially purified protein corresponding to the amino acid sequence of 6 to 97 of (SEQ ID NO:24).

21. A substantially purified protein corresponding to the amino acid sequence of 180 to 257 of (SEQ ID NO:24).

22. A substantially purified protein corresponding to the amino acid sequence of 272 to 349 of (SEQ ID NO:24).

23. A substantially purified protein corresponding to the amino acid sequence of 362 to 444 of (SEQ ID NO:24).

24. A pharmaceutical composition comprising a nucleic acid molecule of claim 1 useful for modulating tumor cell proliferation, cell migration and metastasis, and sterоid hormone receptor function.

25. A method of modulating tumor cell proliferation, cell migration and metastasis, and steroid hormone receptor function by administering a nucleic acid molecule of claim 1.

BNSDOCID <WO 0014106A1 I >

26. A pharmaceutical composition comprising a substantially purified BAG family protein comprising of the amino acid sequence selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24), or a fragment, a derivative or a mimetic thereof, useful for modulating tumor cell proliferation, cell migration and metastasis, and steroid hormone receptor function.

27. A method of modulating tumor cell proliferation by administering a pharmaceutical composition of claim 26.

28. A method of modulating cell migration and metastasis by administering a pharmaceutical composition of claim 26.

29. A method of modulating steroid hormone receptor function by administering a pharmaceutical composition of claim 26.

30. A substantially purified antibody that specifically binds to a BAG family protein of claim 14.

31. The antibody of claim 30, wherein said antibody is a monoclonal antibody.

BNSDOCID <WO__0014106A1 ! >

32. A method for detecting the presence of a BAG family protein in a sample, comprising the steps of:

a. obtaining the sample;

b. adding to said an antibody of claim 11 under suitable conditions for the binding of said antibody with the BAG family protein; and

c. detecting said bound BAG family protein.

33. A method for detecting the presence of a first nucleic acid molecule that encodes a BAG family protein in a sample, comprising the steps of:

a. obtaining the sample;

b. adding to said sample a second nucleic acid molecule capable of hybridizing with said first nucleic acid molecule under suitable conditions for the binding of said second nucleic acid molecule with said first nucleic acid molecule; and

c. detecting said hybridized first and second nucleic acid molecules.

34. A method of determining the risk of metastatic spread of cancer or prognosis of cancer patients by determining the level of expression of a BAG-family protein.

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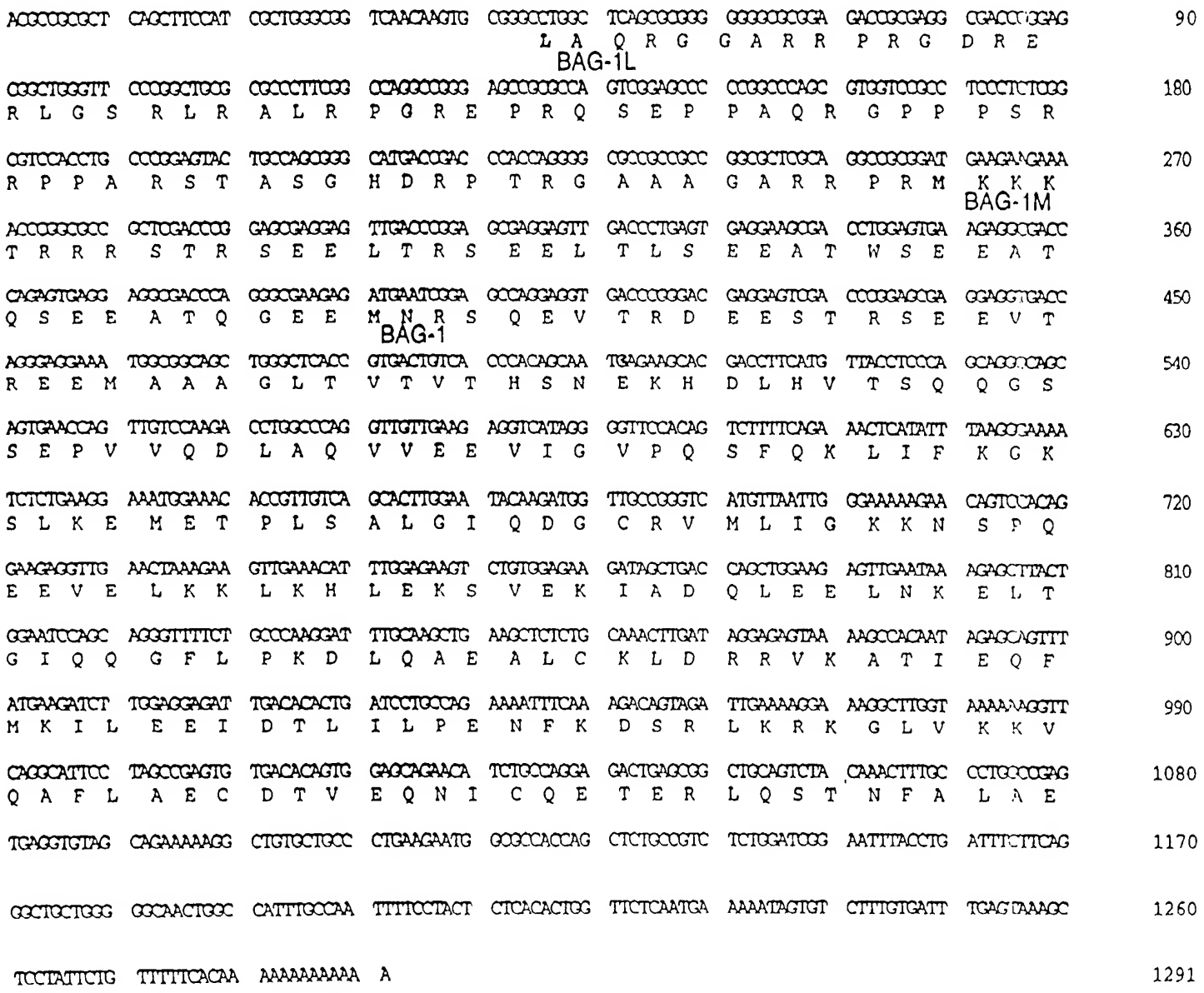


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CGTCCACCTG CCCGGAGTAC TGCCAGCGGG CATGACCGAC CCACCAGGGG CGCCGCCGCC GGCGCTCGCA GGCGGCGGAT GAAGAAGAAA     270

ACCCGGCGCC GCTCGACCCG GAGCGAGGAG TTGACCCGGA GCGAGGAGTT GACCCTGAGT GAGGAAGCGA CCTGGAGTGA AGAGGCGACC     360

CAGAGTGAGG AGGCGACCCA GGGCGAAGAG ATGAATCGGA GCCAGGAGGT GACCCCGGAC GAGGAGTCGA CCCGGAGCGA GGAGGTGACC     450

AGGGAGGAAA TGGCGGCAGC TGGGCTCACC GTGACTGTCA CCCACAGCAA TGAGAAGCAC GACCTTCATG TTACCTCCCA GCAGGGCAGC     540

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TCTCTGAAGG AAATGGAAAC ACCGTTGTCA GCACTTGGAA TACAAGATGG TTGCCGGGTC ATGTTAATTG GGAAAAAGAA CAGTCCACAG     720

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GGCTGCTGGG GGCAACTGGC CATTTGCCAA TTTTCCTACT CTCACACTGG TTCTCAATGA AAAATAGTGT CTTTGTGATT TGAGTAAAGC    1260

TCCTATTCTG TTTTTCACAA AAAAAAAAA A                                                                    1291
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SUBSTITUTE SHEET (RULE 26)

FIGURE 2A

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                                                                                                                    90
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                                                                                  .  M  A  Q  A  K  I  N

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A  K  A  N  E  G  R  F  C  R  S  S  S  M  A  D  R  S  S  R  L  L  E  S  L  D  Q  L  E  L

AGGGTTGAAG CTTTGAGAGA AGCAGCAACT GCTGTTGAGC AAGAGAAAGA AATCCTTCTG GAAATGATCC ACAGTATCCA AAATAGCCAG   360
R  V  E  A  L  R  E  A  A  T  A  V  E  Q  E  K  E  I  L  L  E  M  I  H  S  I  Q  N  S  Q

GACATGAGGC AGATCAGTGA CGGAGAAAGA GAAGAATTAA ATCTGACTGC AAACCGTTTG ATGGGAAGAA CTCTCACCGT TGAAGTGTCA   450
D  M  R  Q  I  S  D  G  E  R  E  E  L  N  L  T  A  N  R  L  M  G  R  T  L  T  V  E  V  S

GTAGAAACAA TTAGAAACCC CCAGCAGCAA GAATCCCTAA AGCATGCCAC AAGGATTATT GATGAGGTGG TCAATAAGTT TCTGGATGAT   540
V  E  T  I  R  N  P  Q  Q  Q  E  S  L  K  H  A  T  R  I  I  D  E  V  V  N  K  F  L  D  D

TTGGGAAATG CCAAGAGTCA TTTAATGTCG CTCTACAGTG CATGTTCATC TGAGGTGCCA CATGGGCCAG TTGATCAGAA GTTTCAATCC   630
L  G  N  A  K  S  H  L  M  S  L  Y  S  A  C  S  S  E  V  P  H  G  P  V  D  Q  K  F  Q  S

ATAGTAATTG GCTGTGCTCT TGAAGATCAG AAGAAAATTA AGAGAAGATT AGAGACTCTG CTTAGAAATA TTGAAAACTC TGACAAGGCC   720
I  V  I  G  C  A  L  E  D  Q  K  K  I  K  R  R  L  E  T  L  L  R  N  I  E  N  S  D  K  A

ATCAAGCTAT TAGAGCATTC TAAAGGAGCT GGTTCCAAAA CTCTGCAACA AAATGCTGAA AGCAGATTCA ATTAGTCTTC AAACCTAAGA   810
I  K  L  L  E  H  S  K  G  A  G  S  K  T  L  Q  Q  N  A  E  S  R  F  N
```

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FIGURE 2B

```
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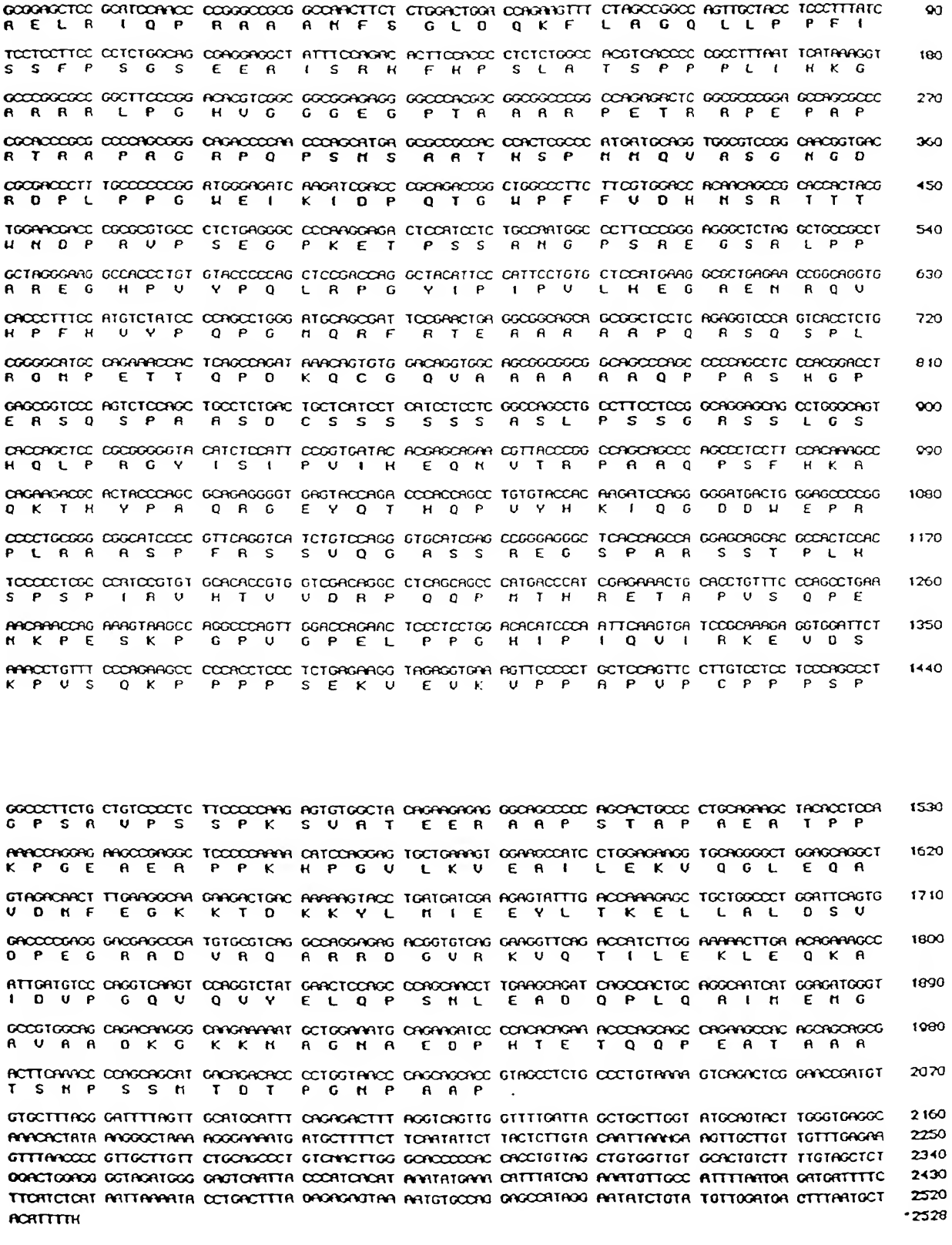
ACGTTCAGCT AGGGGCAAAA AGCATGACTG CTTTTTCCTG TCTGGCATGG AATCACGCAG TCACCTTGGG CATTTAGTTT ACTAGAAATT  1170
CTTTACTGG                                                                                           1179
```

FIGURE 3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R D P L P P G W E I K I D P Q T G W P F F V D H N S R T T T
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W N D P R V P S E G P K E T P S S A N G P S A E G S A L P P
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R G M P E T T Q P D K Q C G Q V A A A A A Q P P A S H G P
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I D V P G Q V Q V Y E L Q P S N L E A D Q P L Q A I M E M G
GCCGTGGCAG CAGACAAGGG CAAGAAAAAT GCTGAAAATG CAGAAGATCC CCACACAGAA ACCCAGCAGC CAGAAGCCAC AGCAGCAGCG 1980
A V A A D K G K K N A G M A E D P H T E T Q Q P E A T A A A
ACTTCAAACC CCAGCAGCAT GACAGACACC CCTGGTAACC CAGCAGCACC GTAGCCTCTG CCCTGTAAAA GTCAGACTCG GAACCGATGT 2070
T S N P S S M T D T P G N P A A P .
GTGCTTTAGG GATTTTAGTT GCATGCATTT CAGAGACTTT AGGTCAGTTG GTTTTGATTA GCTGCTTGGT ATGCAGTACT TGGGTGAGGC 2160
AAACACTATA AAGGGCTAAA AGGGAAAATG ATGCTTTTCT TCAATATTCT TACTCTTGTA CAATTAAACA AGTTGCTTGT TGTTTGAGAA 2250
GTTTAACCCC GTTGCTTGTT CTGCAGCCCT GTCAACTTGG GCACCCCCAC CACCTGTTAG CTGTGGTTGT GCACTGTCTT TTGTAGCTCT 2340
CCACTGCAAG GCTAGATGGG GAGTCAATTA CCCATCACAT AAATATGAAA CATTTATCAG AAATGTTGCC ATTTTAATGA GATGATTTTC 2430
TTCATCTCAT AATTAAAATA CCTGACTTTA CAGAGAGTAA AATGTGCCAG GAGCCATAGG AATATCTGTA TGTTGGATGA CTTTAATGCT 2520
ACATTTTA *2528

FIGURE 4

```
ACGATATCCT GTAAGACCAA GAATTGCAAG GCCAGAGTTT GAATTCTTAT ACAAATGGAG CGTATGGTCC AACATACCCC CCAGGCCCTG     90
GGGCAAATAC TGCCTCATAC TCAGGGGCTT ATTATGCACC TGGTTATACT CAGACCAGTT ACTCCACAGA AGTTCCAAGT ACTTACCGTT    180
CATCTGGCAA CAGCCCAACT CCAGTCTCTC GTTGGATCTA TCCCCAGCAG GACTGTCAAG ACTGAAGCAC CCCCTCTTAA GGGGCAGGTT    270
CCAGGATATC CGCCTTCACA GAACCCTGGA ATGACCCTGC CCCATTATCC TTATGGAGAT GGTAATCGTA GTGTTCCACA ATCACGGCCG    360
                                                  M  E  M  V  I  V  V  F  H  N  H  G  R

ACTGTACGAC CACAAGAAAG ATGCGTGGGC TTCTCCTGGT GCTTATGGAA TGGGTGGCCG TTATCCCTGG CCTTCATCAG CGCCCTCAGC    450
 L  Y  D  H  K  K  D  A  W  A  S  P  G  A  Y  G  M  G  G  R  Y  P  W  P  S  S  A  P  S  A
ACCACCCGGC AATCTCTACA TGACTGAAAG TACTTCACCA TGGCCTAGCA GTGGCTCTCC CCAGTCACCC CCTTCACCCC CAGTCCAGCA    540
 P  P  G  N  L  Y  M  T  E  S  T  S  P  W  P  S  S  G  S  P  Q  S  P  P  S  P  P  V  Q  Q
GCCCAAGGAT TCTTCATACC CCTATAGCCA ATCAGATCAA AGCATGAACC GGCACAACTT TCCTTGCAGT GTCCATCAGT ACGAATCCTC    630
 P  K  D  S  S  Y  P  Y  S  Q  S  D  Q  S  M  N  R  H  N  F  P  C  S  V  H  Q  Y  E  S  S
GGGGACAGTG AACAATGATG ATTCAGATCT TTTGGATTCC CAAGTCCAGT ATAGTGCTGA GCCTCAGCTG TATGGTAATG CCACCAGTGA    720
 G  T  V  N  N  D  D  S  D  L  L  D  S  Q  V  Q  Y  S  A  E  P  Q  L  Y  G  N  A  T  S  D
CCATCCCAAC AATCAAGATC AAAGTAGCAG TCTTCCTGAA GAATGTGTAC CTTCAGATGA AAGTACTCCT CCGAGTATTA AAAAAATCAT    810
 H  P  N  N  Q  D  Q  S  S  S  L  P  E  E  C  V  P  S  D  E  S  T  P  P  S  I  K  K  I  I
ACATGTGCTG GAGAAGGTCC AGTATCTTGA ACAAGAAGTA GAAGAATTTG TAGGAAAAAA GACAGACAAA GCATACTGGC TTCTGGAAGA    900
 H  V  L  E  K  V  Q  Y  L  E  Q  E  V  E  E  F  V  G  K  K  T  D  K  A  Y  W  L  L  E  E
AATGCTAACC AAGGAACTTT TGGAACTGGA TTCAGTTGAA ACTGGGGGCC AGGACTCTGT ACGGCAGGCC AGAAAAGAGG CTGTTTGTAA    990
 M  L  T  K  E  L  L  E  L  D  S  V  E  T  G  G  Q  D  S  V  R  Q  A  R  K  E  A  V  C  K
GATTCAGGCC ATATTGGAAA                                                                             1010
 I  Q  A  I  L  E
```

BNSDOCID <WO 0014106A1_I_>

FIGURE 5

```
GAGAAATAAA AAATGAACTT CTCCAAGCAC AAAACCCTTC TGAATTGTAC CTGAGCTCCA AAACAGAATT GCAGGGTTTA ATTGGACAGT    90
  E  I  K  N  E  L  L  Q  A  Q  N  P  S  E  L  Y  L  S  S  K  T  E  L  Q  G  L  I  G  Q  L

TGGATGAGGT AAGTNTTGAA AAAAACCCCT GCATCCGGGA AGCCAGGAGA AGAGCAGTGA TCGAGGTGCA AACTCTGATC ACATATATTG   180
  D  E  U  S  X  E  K  N  P  C  I  R  E  A  R  R  R  A  U  I  E  U  Q  T  L  I  T  Y  I  D

ACTTGAAGGA GGCCCTTGAG AAAAGAAAGC TGTTTGCTTG TGAGGAGCAC CCATCCCATA AAGCCGTCTG GAACGTCCTT GGAAACTTGT   270
  L  K  E  A  L  E  K  R  K  L  F  A  C  E  E  H  P  S  H  K  A  U  W  N  U  L  G  N  L  S

CTGAGATCCA GGGAGAAGTT CTTTCATTTG ATGGAAATCG AACCGATAAG AACTACATCC GGCTGGAAGA GCTGCTCACC AAGCAGCTGC   360
  E  I  Q  G  E  U  L  S  F  D  G  N  R  T  D  K  N  Y  I  R  L  E  E  L  L  T  K  Q  L  L

TAGCCCTGGA TGCTGTTGAT CCGCAGGGAG AAGAGAAGTG TAAGGCTGCC AGGAAACAAG CTGTGAGGCT TGCGCAGAAT ATTCTCAGCT   450
  A  L  D  A  U  D  P  Q  G  E  E  K  C  K  A  A  R  K  Q  A  U  R  L  A  Q  N  I  L  S  Y

ATCTCGACCT GAAATCTGAT GAATGGGAGT ACTGAAATAC CAGAGATCTC ACTTTTGATA CTGTTTTGCA CTTCATATGT GCTTCTATGT   540
  L  D  L  K  S  D  E  W  E  Y  .
ATAGAGAGCT TTCAGTTCAT TGATTTATAC GTGCATATTT CAGTCTCAGT ATTTATGATT GAAGCAAATT CTATTCAGTA TCTGCTGCTT   630

TTGATGTTGC AAGACAAATA TCATTACAGC ACGTTAACTT TTCCATTCGG ATCAAAAAA                                       689
```

FIGURE 6A

ATGTCTTTCCGCCTCTTCGTTGAAATATTTCACTTTCTTTTCCAGCTTTTTCCCCATCTCGACCT
GCTTTGGTTTTT
CGAGAAAACCACGTTCCAAATCAGCGACATCTCTCAAATTGAGATCATAGGCTTTTTGAAGATTG
CTCAAATTATG
CTTCTCATATTGCATGAGCATTTTGAAGCCCGCGTCATCAACCAAAGCATTTTTTCCACCCATCA
CAATGATTTTAT CATTTTCTTTAAAATT

BNSDOCID <WC___0014106A1 | >

FIGURE 6B

```
MKVNVSCSSV QTTIDILEEN QGEDESILTL GQLRDRIATD NDVDVETMKL      50
LHRGKFLQGA DDVSLSTLNF KENDKIIVMG GKNALVDDAG FKMLMQYEKH     100
NLSNLQKAYD LNLRDVADLE RGFLEKPKQV EMGKKLEKKV KYFNEEAERH     150
LETLDGMNII TETTPENQAK RNREKRKTLV NGIQTLLNQN DALLRRLQEY     200
QSVLNGDIPE                                                 210
```

BNSDOCID <WO 0014106A1 | >

FIGURE 7A

```
ATGCCAGTCG TGAACATACC AATCAAAATA CTTGGTCAGA ATCAATCACA      50
TAGTCGAAGT AACTCCTCGT CTTCTGTTGA CAACGATCGA AATCAACCAC     100
CACAGCAGCC ACCTCAACCG CAACCACAAC AGCAATCTCA GCAACAATAC     150
CAGCAGGCTC CAAACGTGAA TACCAATATG CATCATTCCA ACGGATTCTC     200
ACCTAACTTC CCATCTCGTA GTCCTATTCC GGACTTTCCC AGTTTTTCAT     250
CTGGGTTCCC AAACGATTCT GAATGGTCTT CGAATTTCCC GTCGTTTCCA     300
AATTTCCCAA GTGGATTCTC AAATGGAAGT TCTAATTTCC CTGATTTTCC     350
AAGATTCGGA AGAGATGGAG GACTATCGCC AAACCCACCG ATGCAAGGAT     400
ACAGGAGAAG TCCAACACCA ACATCAACTC AATCTCCAAC TTCTACATTA     450
AGACGCAACT CTCAGCAGAA TCAAGCTCCT CCACAATATT CTCAGCAACA     500
ACCACAACAA GCTCAACAAC GTCAGACAAC TCCTCCGTCA ACAAAAGCTT     550
CATCTCGACC ACCATCTCGT ACTCGTGAAC CAAAGGAACC TGAGGTACCC     600
GAGAGACCAG CAGTTATTCC ATTGCCATAT GAGAAGAAGG AGAAACCACT     650
GGAGAAGAAA GGTAGTCGTG ATTCTGGAAA GGGTGATGAG AACCTTGAAG     700
AGAACATTGC CAAGATCACG ATCGGAAAGA ATAATTGCGA GTTATGTCCG     750
GAACAAGAAA CGGACGGCGA CCCATCTCCA CTAACCTCCC CAATCACCGA     800
AGGAAAGCCA AAGAGAGGAA AGAAACTTCA ACGTAATCAA AGTGTTGTTG     850
ATTTCAATGC CAAGACAATT GTTACTTTGG ATAAAATTGA ATTACAAGTT     900
GAGCAGTTGA GAAAAAAAGC TGCTGAACTC GAAATGGAAA AAGAGCAAAT     950
TCTTCGTTCT CTAGGAGAAA TCAGTGTTCA TAACTGCATG TTCAAACTGG    1000
AAGAATGTGA TCGTGAAGAG ATTGAAGCAA TCACTGACCG ATTGACAAAA    1050
AGAACAAAGA CAGTTCAAGT TGTTGTCGAA ACTCCACGAA ATGAAGAACA    1100
GAAAAAAGCA CTGGAAGATG CAACTTTGAT GATCGATGAA GTCGGAGAAA    1150
TGATGCATTC GAATATTGAA AAGGCTAAGC TGTGCCTACA AACCTACATG    1200
AACGCCTGTT CGTACGAAGA AACTGCTGGA GCCACCTGCC AAAACTTCTT    1250
GAAGATCATA ATTCAGTGCG CTGCTGATGA TCAGAAACGC ATCAAGCGTC    1300
GTCTGGAAAA TCTGATGTCT CAAATTGAGA ATGCTGAGAG AACGAAAGCA    1350
GATTTGATGG ATGATCAAAG CGAATAG                             1377
```

FIGURE 7B

```
MPVVNIPIKI LGQNQSHSRS NSSSSVDNDR NQPPQQPPQP QPQQQSQQQY      50
QQAPNVNTNM HHSNGFSPNF PSRSPIPDFP SFSSGFPNDS EWSSNFPSFP     100
NFPSGFSNGS SNFPDFPRFG RDGGLSPNPP MQGYRRSPTP TSTQSPTSTL     150
RRNSQQNQAP PQYSQQQPQQ AQQRQTTPPS TKASSRPPSR TREPKEPEVP     200
ERPAVIPLPY EKKEKPLEKK GSRDSGKGDE NLEENIAKIT IGKNNCELCP     250
EQETDGDPSP LTSPITEGKP KRGKKLQRNQ SVVDFNAKTI VTLDKIELQV     300
EQLRKKAAEL EMEKEQILRS LGEISVHNCM FKLEECDREE IEAITDRLTK     350
RTKTVQVVVE TPRNEEQKKA LEDATLMIDE VGEMMHSNIE KAKLCLQTYM     400
NACSYEETAG ATCQNFLKII IQCAADDQKR IKRRLENLMS QIENAERTKA     450
DLMDDQSE                                                   458
```

BNSDOCID <WO 0014106A1 I >

FIGURE 8A

```
ATGTCAGAAA AGACTAGCAC AGTTACAATA CACTATGGAA ATCAGCGATT      50
TCCGGTAGCA GTCAATCTAA ATGAGACGTT AAGTGAACTG ATTGATGATT     100
TACTTGAAAC GACTGAGATT TCTGAGAAGA AAGTCAAGCT TTTTTACGCT     150
GGCAAGCGTT TAAAAGACAA AAAAGCCTCG TTATCAAAAT TGGGTTTAAA     200
AAATCATAGT AAAATTCTAT GTATAAGACC ACATAAGCAA CAACGAGGTT     250
CCAAGGAAAA AGACACGGTT GAGCCCGCTC CGAAAGCGGA AGCGGAGAAT     300
CCTGTATTTT CGCGTATTTC TGGAGAAATA AAAGCCATCG ATCAGTATGT     350
TGACAAAGAA CTTTCCCCCA TGTACGACAA TTACGTAAAT AAACCGTCGA     400
ACGATCCAAA GCAGAAAAAC AAACAGAAAC TAATGATAAG TGAACTACTT     450
TTACAACAGC TTTTAAAATT GGATGGAGTT GACGTACTGG GCAGCGAGAA     500
ATTGCGTTTT GAACGGAAGC AACTTGTTTC TAAGATCCAA AAAATGTTGG     550
ATCACGTTGA CCAAACAAGC CAAGAAGTGG CCGCATAG                  588
```

FIGURE 8B

```
MSEKTSTVTI HYGNQRFPVA VNLNETLSEL IDDLLETTEI SEKKVKLFYA      50
GKRLKDKKAS LSKLGLKNHS KILCIRPHKQ QRGSKEKDTV EPAPKAEAEN     100
PVFSRISGEI KAIDQYVDKE LSPMYDNYVN KPSNDPKQKN KQKLMISELL     150
LQQLLKLDGV DVLGSEKLRF ERKQLVSKIQ KMLDHVDQTS QEVAA          195
```

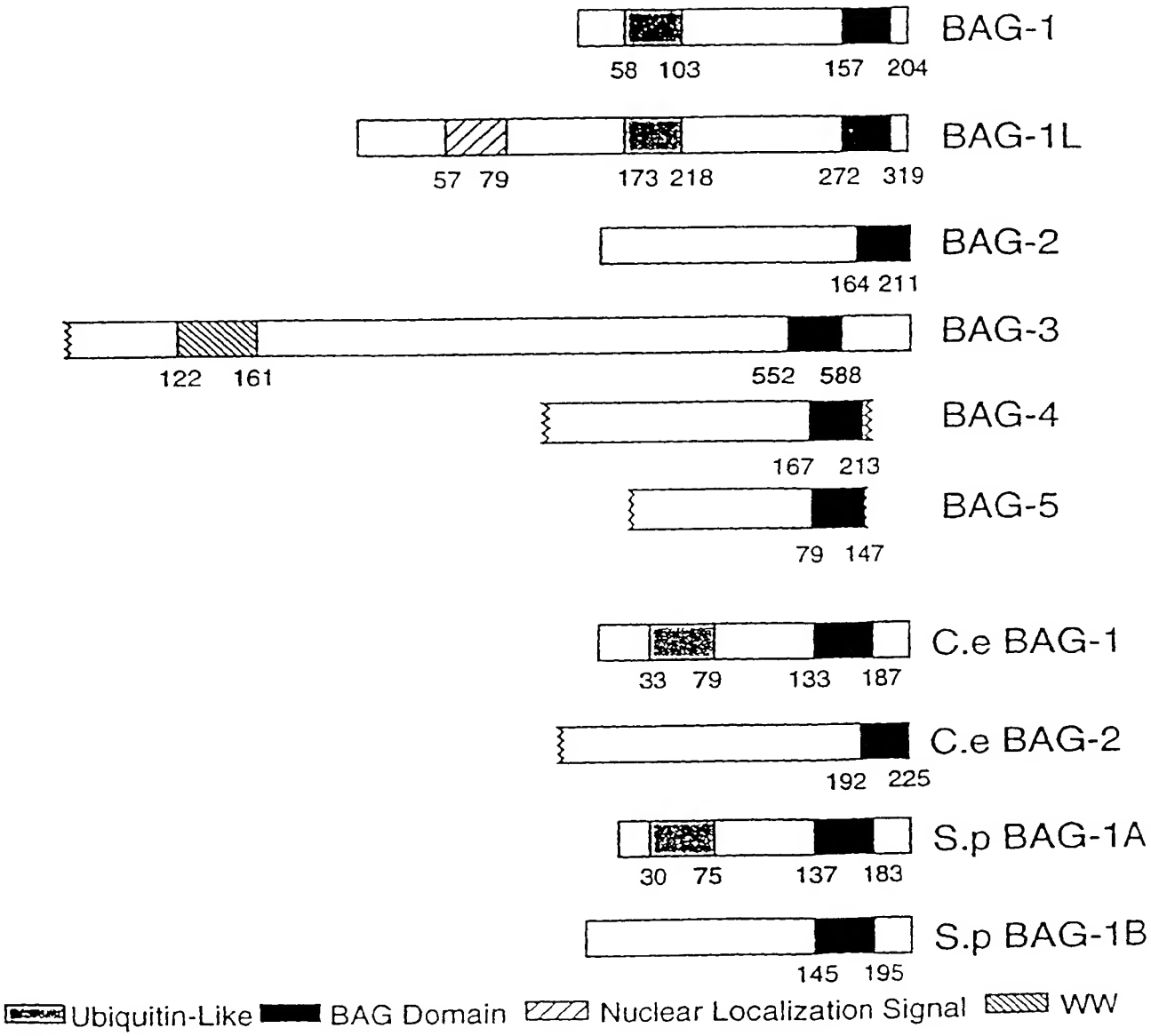
FIGURE 9A

```
ATGTCTTTTT TTACCCAGTT GTGTTCTATG GATAAAAAAT ATTGGATCTC      50
TCTAGCTGTA TTGTCAGTTA CTGTTTTGAT TAGCGCATTA TTGAAAAAGA     100
GAGCTACTGA AACCGAAGAT ATTGTCGTTG TTCATTACGA TGGCGAAAAG     150
TTGAATTTTG TGTTGCGACA ACCAAGGCTG AATATGGTTT CTTACACTAG     200
TTTTCTTCGT CGCGTGTGCA ACGCATTTTC AGTAATGCCC GACAAAGCGT     250
CTCTCAAGTT AAACGGGGTG ACCCTCAAGG ATGGTTCACT TTCCGACCAA     300
AATGTGCAAA ATGGAAGTGA ATTAGAGCTC GAATTACCCA AACTGAGCCC     350
GGCAATGCAA CAAATTGAAG CATATATAGA TGAGCTTCAA CAGGATCTCG     400
TCCCTAAAAT TGAAGCCTTC TGCCAATCGT CTCCCGCTTC GGCACAAGAT     450
GTTCAAGATT TGCATACACG CCTTAGTGAA ACATTGTTGG CTAGGATGAT     500
AAAATTAGAT GCTGTTAATG TTGAAGACGA CCCAGAAGCT CGTCTTAAAA     550
GAAAAGAAGC TATTCGTTTA TCTCAACAAT ATTTGAGTAA ACTAGATTCC     600
ACCAAGAATC AAAACAAATG A                                    621
```

FIGURE 9B

```
MSFFTQLCSM DKKYWISLAV LSVTVLISAL LKKRATETED IVVVHYDGEK      50
LNFVLRQPRL NMVSYTSFLR RVCNAFSVMP DKASLKLNGV TLKDGSLSDQ     100
NVQNGSELEL ELPKLSPAMQ QIEAYIDELQ QDLVPKIEAF CQSSPASAQD     150
VQDLHTRLSE TLLARMIKLD AVNVEDDPEA RLKRKEAIRL SQQYLSKLDS     200
TKNQNK                                                     206
```

FIGURE 10A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58 103
157 204
BAG-1L
57 79
173 218
272 319
BAG-2
164 211
BAG-3
122 161
552 588
BAG-4
167 213
BAG-5
79 147
C.e BAG-1
33 79
133 187
C.e BAG-2
192 225
S.p BAG-1A
30 75
137 183
S.p BAG-1B
145 195
Ubiquitin-Like
BAG Domain
Nuclear Localization Signal
WW

FIGURE 10B

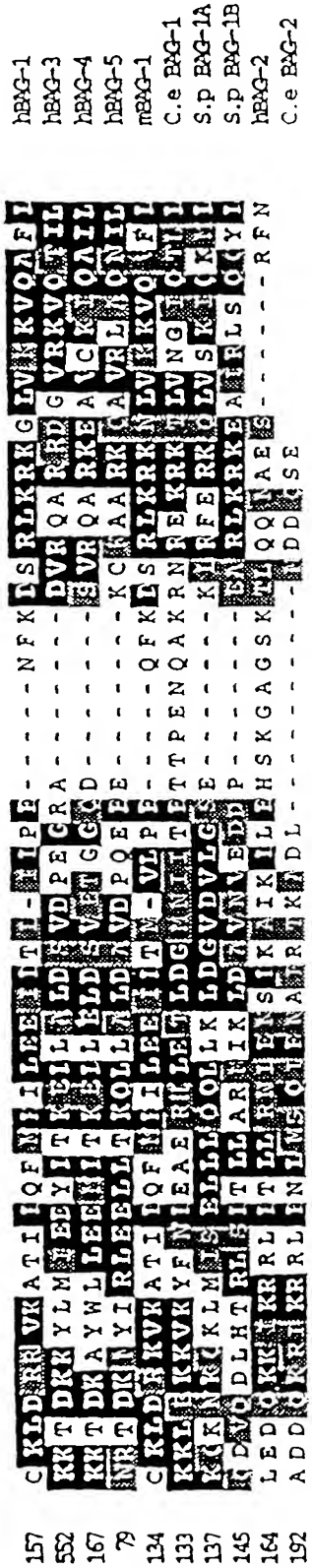

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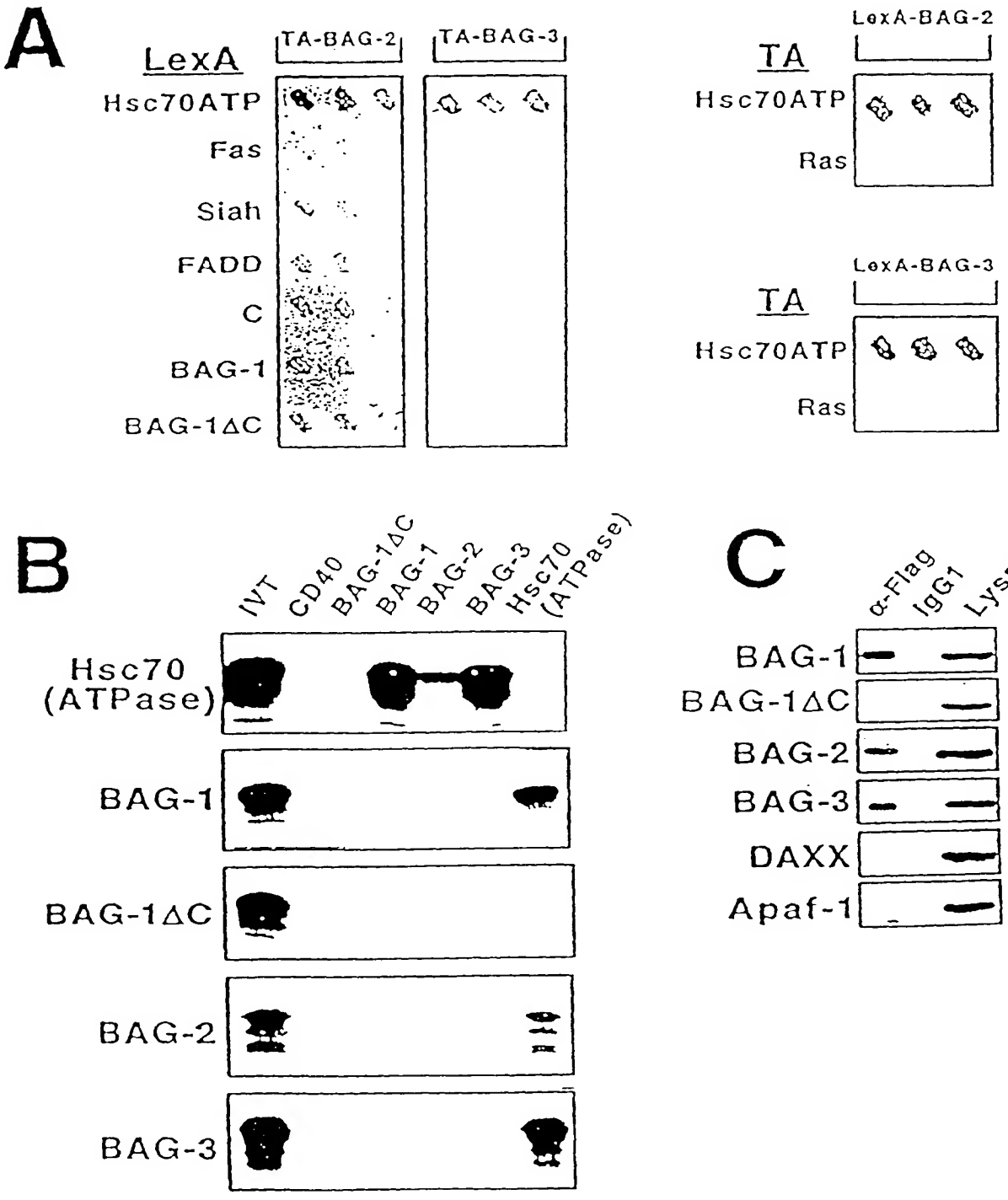
FIGURE 11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TA-BAG-2
TA-BAG-3
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Fas
Siah
FADD
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LexA-BAG-2
TA
Hsc70ATP
Ras
LexA-BAG-3
TA
Hsc70ATP
Ras
B
IVT
CD40
BAG-1ΔC
BAG-1
BAG-2
BAG-3
Hsc70 (ATPase)
Hsc70 (ATPase)
BAG-1
BAG-1ΔC
BAG-2
BAG-3
C
α-Flag
IgG1
Lysate
BAG-1
BAG-1ΔC
BAG-2
BAG-3
DAXX
Apaf-1

FIGURE 12

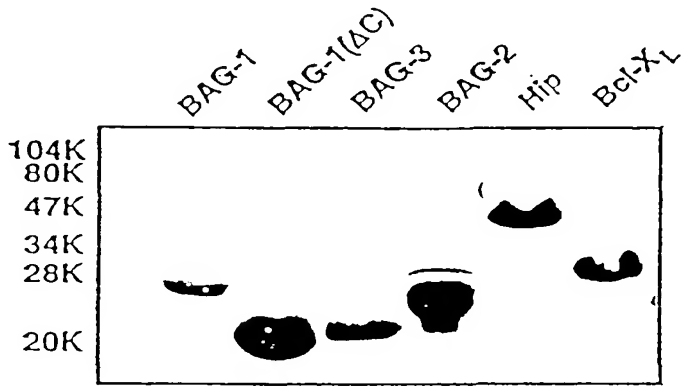
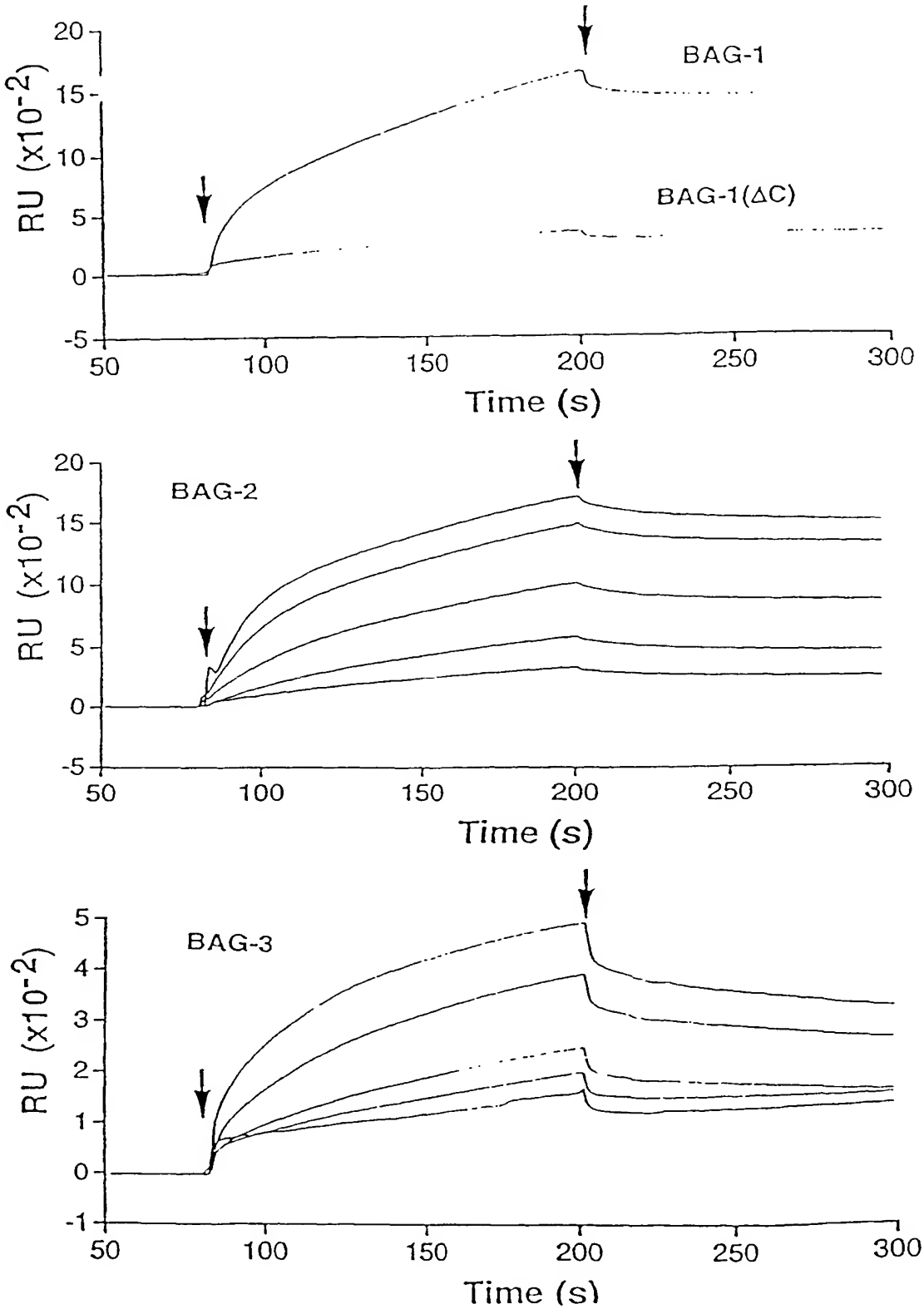


FIGURE 13


BAG-1
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RU (x10-2)
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BAG-2
RU (x10-2)
Time (s)
BAG-3
RU (x10-2)
Time (s)

FIGURE 14

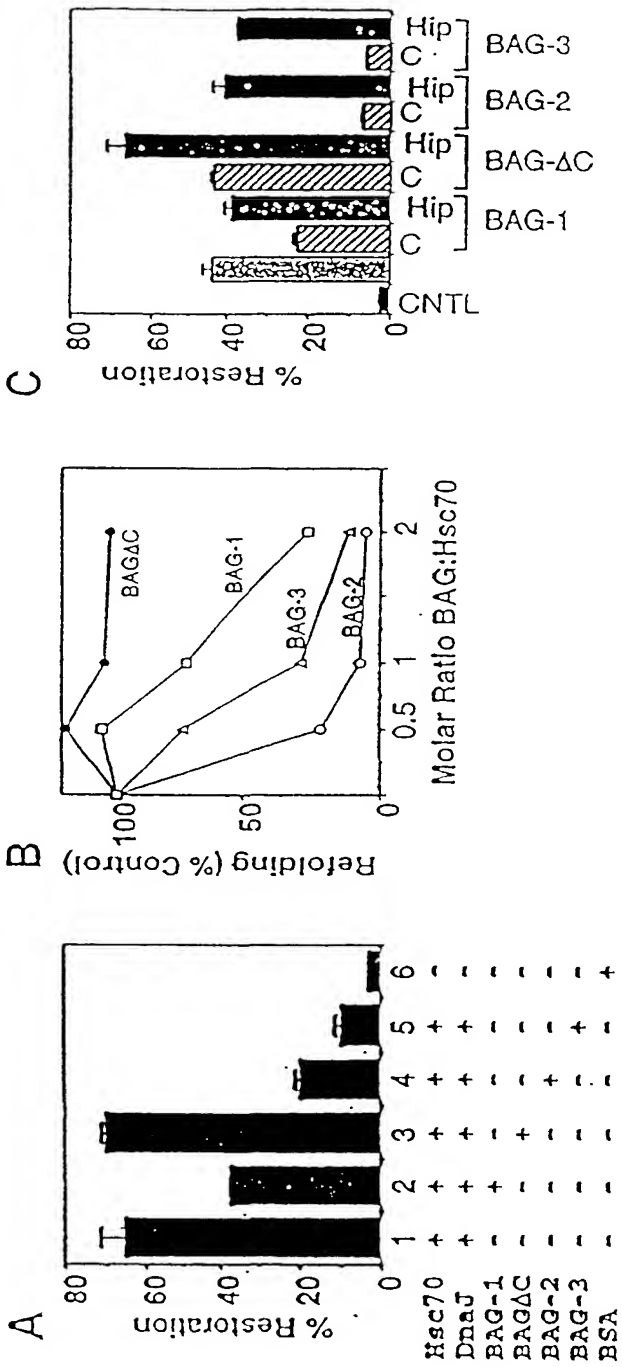

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FIGURE 15A

GCGGAGCTCC GCATCCAACC CCGGGCCGCG GCCAACTTCT CTGGACTGGA 50
CCAGAAGTTT CTAGCCGGCC AGTTGCTACC TCCCTTTATC TCCTCCTTCC 100
CCTCTGGCAG CGAGGAGGCT ATTTCCAGAC ACTTCCACCC CTCTCTGGCC 150
ACGTCACCCC CGCCTTTAAT TCATAAAGGT GCCCGGCGCC GGCTTCCCGG 200
ACACGTCGGC GGCGGAGAGG GGCCCACGGC GGCGGCCCGG CCAGAGACTC 250
GGCGCCCGGA GCCAGCGCCC CGCACCCGCG CCCCAGCGGG CAGACCCCAA 300
CCCAGCATGA GCGCCGCCAC CCACTCGCCC ATGATGCAGG TGGCGTCCGG 350
CAACGGTGAC CGCGACCCTT TGCCCCCCGG ATGGGAGATC AAGATCGACC 400
CGCAGACCGG CTGGCCCTTC TTCGTGGACC ACAACAGCCG CACCACTACG 450
TGGAACGACC CGCGCGTGCC CTCTGAGGGC CCCAAGGAGA CTCCATCCTC 500
TGCCAATGGC CCTTCCCGGG AGGGCTCTAG GCTGCCGCCT GCTAGGGAAG 550
GCCACCCTGT GTACCCCCAG CTCCGACCAG GCTACATTCC CATTCCTGTG 600
CTCCATGAAG GCGCTGAGAA CCGGCAGGTG CACCCTTTCC ATGTCTATCC 650
CCAGCCTGGG ATGCAGCGAT TCCGAACTGA GGCGGCAGCA GCGGCTCCTC 700
AGAGGTCCCA GTCACCTCTG CGGGGCATGC CAGAAACCAC TCAGCCAGAT 750
AAACAGTGTG GACAGGTGGC AGCGGCGGCG GCAGCCCAGC CCCCAGCCTC 800
CCACGGACCT GAGCGGTCCC AGTCTCCAGC TGCCTCTGAC TGCTCATCCT 850
CATCCTCCTC GGCCAGCCTG CCTTCCTCCG GCAGGAGCAG CCTGGGCAGT 900
CACCAGCTCC CGCGGGGGTA CATCTCCATT CCGGTGATAC ACGAGCAGAA 950
CGTTACCCGG CCAGCAGCCC AGCCCTCCTT CCACAAAGCC CAGAAGACGC 1000
ACTACCCAGC GCAGAGGGGT GAGTACCAGA CCCACCAGCC TGTGTACCAC 1050
AAGATCCAGG GGGATGACTG GGAGCCCCCG CCCCTGCGGG CGGCATCCCC 1100
GTTCAGGTCA TCTGTCCAGG GTGCATCGAG CCGGGAGGGC TCACCAGCCA 1150
GGAGCAGCAC GCCACTCCAC TCCCCCTCGC CCATCCGTGT GCACACCGTG 1200
GTCGACAGGC CTCAGCAGCC CATGACCCAT CGAGAAACTG CACCTGTTTC 1250
CCAGCCTGAA AACAAACCAG AAAGTAAGCC AGGCCCCAGTT GGACCAGAAC 1300
TCCCTCCTGG ACACATCCCA ATTCAAGTGA TCCGCAAAGA GGTGGATTCT 1350

BNSDOCID <WO_0014106A1 I_>

FIGURE 15A

AAACCTGTTT CCCAGAAGCC CCCACCTCCC TCTGAGAAGG TAGAGGTGAA 1400
AGTTCCCCCT GCTCCAGTTC CTTGTCCTCC TCCCAGCCCT GGCCCTTCTG 1450
CTGTCCCCTC TTCCCCCCAAG AGTGTGGCTA CAGAAGAGAG GGCAGCCCCC 1500
AGCACTGCCC CTGCAGAAGC TACACCTCCA AAACCAGGAG AAGCCGAGGC 1550
TCCCCCAAAA CATCCAGGAG TGCTGAAAGT GGAAGCCATC CTGGAGAAGG 1600
TGCAGGGGCT GGAGCAGGCT GTAGACAACT TTGAAGGCAA GAAGACTGAC 1650
AAAAAGTACC TGATGATCGA AGAGTATTTG ACCAAAGAGC TGCTGGCCCT 1700
GGATTCAGTG GACCCCGAGG GACGAGCCGA TGTGCGTCAG GCCAGGAGAG 1750
ACGGTGTCAG GAAGGTTCAG ACCATCTTGG AAAAACTTGA ACAGAAAGCC 1800
ATTGATGTCC CAGGTCAAGT CCAGGTCTAT GAACTCCAGC CCAGCAACCT 1850
TGAAGCAGAT CAGCCACTGC AGGCAATCAT GGAGATGGGT GCCGTGGCAG 1900
CAGACAAGGG CAAGAAAAAT GCTGGAAATG CAGAAGATCC CCACACAGAA 1950
ACCCAGCAGC CAGAAGCCAC AGCAGCAGCG ACTTCAAACC CCAGCAGCAT 2000
GACAGACACC CCTGGTAACC CAGCAGCACC GTAGCCTCTG CCCTGTAAAA 2050
ATCAGACTCG GAACCGATGT GTGCTTTAGG GAATTTTAAG TTGCATGCAT 2100
TTCAGAGACT TTAAGTCAGT TGGTTTTTAT TAGCTGCTTG GTATGCAGTA 2150
ACTTGGGTGG AGGCAAAACA CTAATAAAAG GGCTAAAAAG GAAAATGATG 2200
CTTTTCTTCT ATATTCTTAC TCTGTACAAA TAAAGAAGTT GCTTGTTGTT 2250
TGAGAAGTTT AACCCCGTTG CTTGTTCTGC AGCCCTGTCT ACTTGGGCAC 2300
CCCCACCACC TGTTAGCTGT GGTTGTGCAC TGTCTTTTGT AGCTCTGGAC 2350
TGGAGGGGTA GATGGGGAGT CAATTACCCA TCACATAAAT ATGAAACATT 2400
TATCAGAAAT GTTGCCATTT TAATGAGATG ATTTTCTTCA TCTCATAATT 2450
AAAATACCTG ACTTTAGAGA GAGTAAAATG TGCCAGGAGC CATAGGAATA 2500
TCTGTATGTT GGATGACTTT AATGCTACAT TTTC 2534

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FIGURE 15B

MSAATHSPMMQVASGNGDRD PLPPGWEIKI DPQTGWPFFV DHNSRTTTWN 50
DPRVPSEGPK ETPSSANGPS REGSRLPPAR EGHPVYPQLR PGYIPIPVLH 100
EGAENRQVHP FHVYPQPGMQ RFRTEAAAAA PQRSQSPLRG MPETTQPDKQ 150
CGQVAAAAAA QPPASHGPER SQSPAASDCS SSSSSASLPS SGRSSLGSHQ 200
LPRGYISIPV IHEQNVTRPA AQPSFHKAQK THYPAQRGEY QTHQPVYHKI 250
QGDDWEPRPL RAASPFRSSV QGASSREGSP ARSSTPLHSP SPIRVHTVVD 300
RPQQPMTHRE TAPVSQPENK PESKPGPVGP ELPPGHIPIQ VIRKEVDSKP 350
VSQKPPPPSE KVEVKVPPAP VPCPPPSPGP SAVPSSPKSV ATEERAAPST 400
APAEATPPKP GEAEAPPKHP GVLKVEAILE KVQGLEQAVD NFEGKKTDKK 450
YLMIEEYLTK ELLALDSVDP EGRADVRQAR RDGVRKVQTI LEKLEQKAID 500
VPGQVQVYEL QPSNLEADQP LQAIMEMGAV AADKGKKNAG NAEDPHTETQ 550
QPEATAAATS NPSSMTDTPG NPAAP 575

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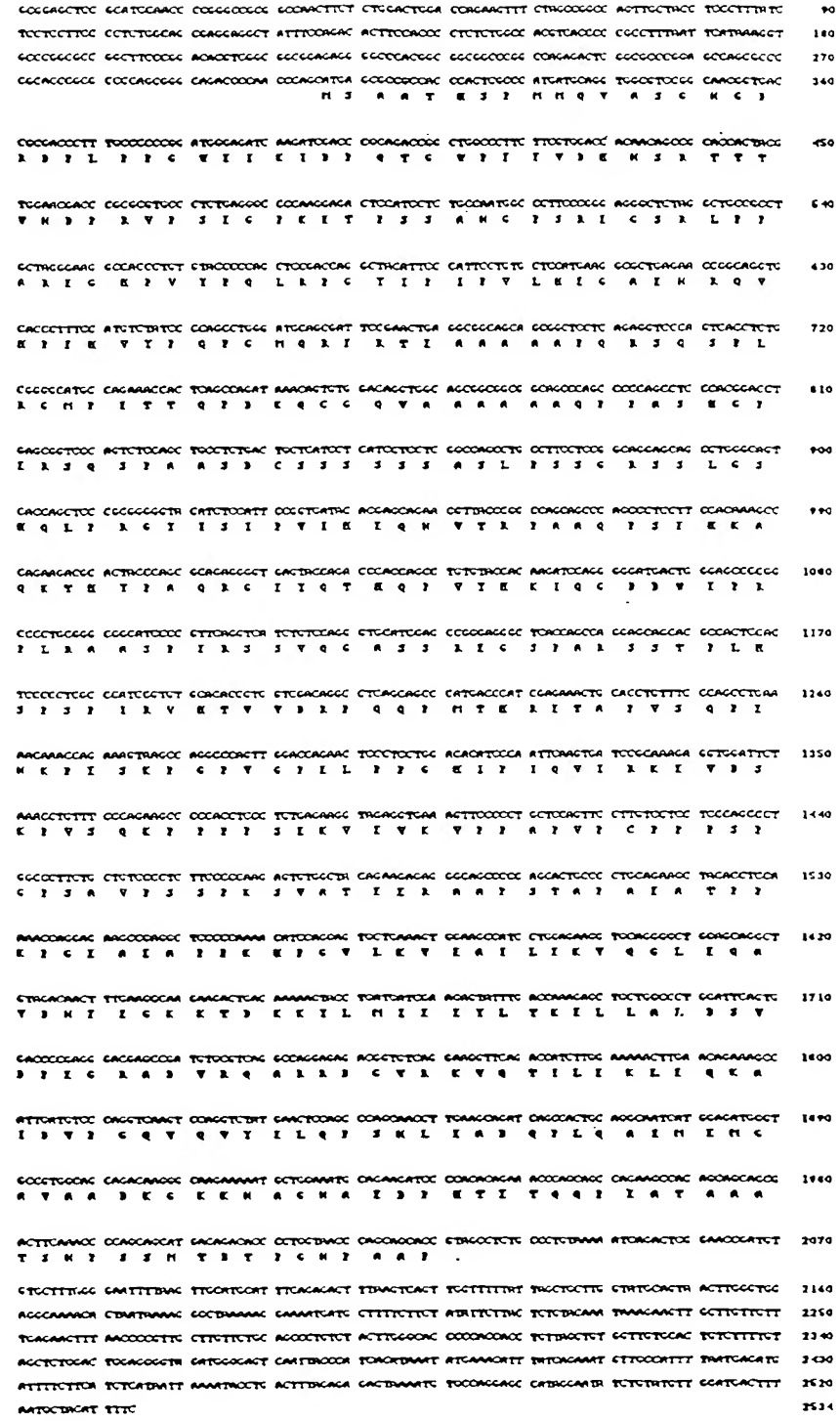
FIGURE 15C



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TATCCTCTTC GCCCTGAACC TCCCCAGCCT CCCATTTCCT GGCGGGTGCG 200
CGGGGGCGGC CCGGCGGAGA CCACCTGGCT GGGAGAAGGC GGAGGAGGCG 250
ATGGCTACTA TCCCTCGGGA GGCGCCTGGC CAGAGCCTGG TCGAGCCGGA 300
GGAAGCCACC AGGAGCAGCC ACCATATCCT AGCTACAATT CTAACTATTG 350
GAATTCTACT GCGAGATCTA GGGCTCCTTA CCCAAGTACA TATCCTGTAA 400
GACCAGAATT GCAAGGCCAG AGTTTGAATT CTTATACAAA TGGAGCGTAT 450
GGTCCAACAT ACCCCCCAGG CCCTGGGGCA AATACTGCCT CATACTCAGG 500
GGCTTATTAT GCACCTGGTT ATACTCAGAC CAGTTACTCC ACAGAAGTTC 550
CAAGTACTTA CCGTTCATCT GGCAACAGCC CAACTCCAGT CTCTCGTTGG 600
ATCTATCCCC AGCAGGACTG TCAGACTGAA GCACCCCCTC TTAGGGGGCA 650
GGTTCCAGGA TATCCGCCTT CACAGAACCC TGGAATGACC CTGCCCCATT 700
ATCCTTATGG AGATGGTAAT CGTAGTGTTC CACAATCAGG ACCGACTGTA 750
CGACCACAAG AAGATGCGTG GGCTTCTCCT GGTGCTTATG GAATGGGTGG 800
CCGTTATCCC TGGCCTTCAT CAGCGCCCTC AGCACCACCC GGCAATCTCT 850
ACATGACTGA AAGTACTTCA CCATGGCCTA GCAGTGGCTC TCCCCAGTCA 900
CCCCCTTCAC CCCCAGTCCA GCAGCCCAAG GATTCTTCAT ACCCCTATAG 950
CCAATCAGAT CAAAGCATGA ACCGGCACAA CTTTCCTTGC AGTGTCCATC 1000
AGTACGAATC CTCGGGGACA GTGATCAATG AAGATTCAGA TCTTTTGGAT 1050
TCCCAAGTCC AGTATAGTGC TGAGCCTCAG CTGTATGGTA ATGCCACCAG 1100
TGACCATCCC AACAATCAAG ATCAAAGTAG CAGTCTTCCT GAAGAATGTG 1150
TACCTTCAGA TGAAAGTACT CCTCCGAGTA TTAAAAAAAT CATACATGTG 1200
CTGGAGAAGG TCCAGTATCT TGAACAAGAA GTAGAAGAAT TTGTAGGAAA 1250
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FIGURE 16A

BNSDOCID <WO_0014106A1_I_>

FIGURE 16A

TTTTGGAACT GGATTCAGTT GAAACTGGGG GCCAGGACTC TGTACGGCAG 1350
GCCAGAAAAG AGGCTGTTTG TAAGATTCAG GCCATACTGG AAAAATTAGA 1400
AAAAAAAGGA TTATGAAAGG ATTTAGAACA AAGTGGAAGC CTGTTACTAA 1450
CTTGACCAAA GAACACTTGA TTAGGTTAAT TACCCTCTTT TTGAAATGCC 1500
TGTTGATGAC AAGAAGCAAT ACATTCCAGC TTTTCCTTTG ATTTTATACT 1550
TGAAAAACTG GCAAAGGAAT GGAAGAATAT TTTAGTCATG AAGTTGTTTT 1600
CAGTTTTCAGA CGAATGAATG TAATAGGAAA CTATGGAGTT ACCAATATTG 1650
CCAAGTAGAC TCACTCCTTA AAAAATTTAT GGATATCTAC AAGCTGCTTA 1700
TTACCAGCAG GAGGGAAACA CACTTCACAC AACAGGCTTA TCAGAAACCT 1750
ACCAGATGAA ACTGGATATA ATTTGAGACA AACAGGATGT GTTTTTTTAA 1800
ACATCTGGAT ATCTTGTCAC ATTTTTGTAC ATTGTGACTG CTTTCAACAT 1850
ATACTTCATG TGTAATTATA GCTTAGACTT TAGCCTTCTT GGACTTCTGT 1900
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AAAAAAAAAA AAAAAA 1966

BNSDOCID <WO 0014106A1 I >

FIGURE 16B

MSALRRSGYGPSDGPSYGRYYGPGGGDVPVHPPPPLYPLRPEPPQPPISWRVRGGPAETTWLGEGGGGDGYYPSGGAWP
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TQTSYSTEVPSTYRSSGNSPTPVSRWMYPQQDCQTEAPPLRGQVPGYPPSQNPGMTLPHYPYGDGNRSVPQSGPTVRPQE
DAWASPGAYGMGGRYPWPSSAPSAPPGNLYMTESTSPWPSSGSPQSPPSPPVQQPKDSSYPYSQSDQSMNRHNFPCSVHQ
YESSGTVINEDSDLLDSQVQYSAEPQLYGNATSDHPNNQDQSSSLPEECVPSDESTPPSIKKIIHVLEKVQYLEQEVEEF
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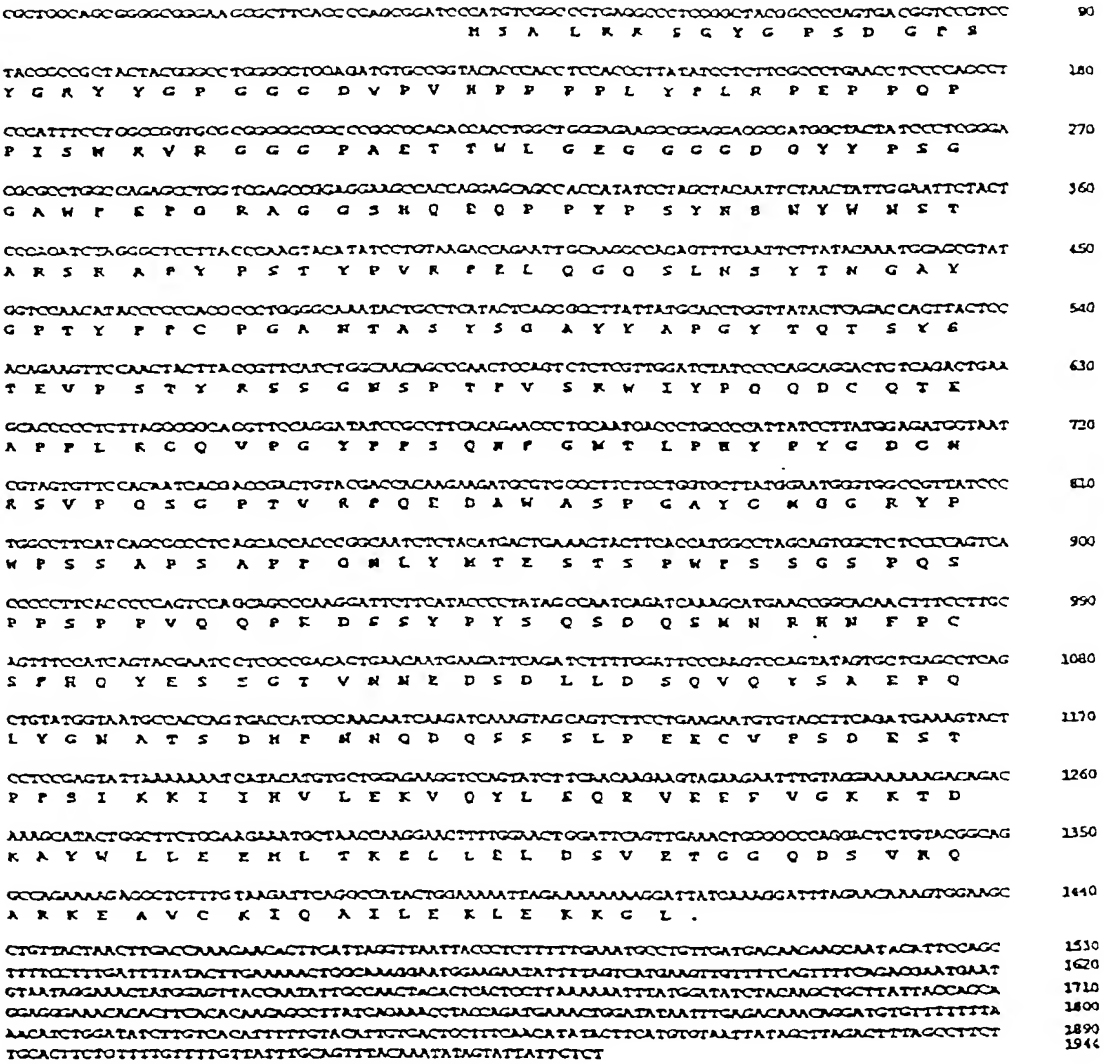
FIGURE 16C



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CAGTAGCGGC CCCTTCACCG GCTGCCCCGC TCAGACCTAG TCGGGAGGGG 100
TGCGAGGCAT GCAGCTGGGG GCCCAGCTCC GGTGCCGCAC CCCGTAAAGG 150
GCTGATCTTC CACCTCGCCA CCTCAGCCAC GGGACGCCAA GACCGCATCC 200
AATTCAGACT TCTTTTGGTG CTTGTGAAAC TGAACACAAC AAAAGTATGG 250
ATATGGGAAA CCAACATCCT TCTATTAGTA GGCTTCAGGA AATCCAAAAG 300
GAAGTAAAAA GTGTAGAACA GCAAGTTATC GGCTTCAGTG GTCTGTCAGA 350
TGACAAGAAT TACAAGAAAC TGGAGAGGAT TCTAACAAAA CAGCTTTTTG 400
AAATAGACTC TGTAGATACT GAAGGAAAAG GAGATATTCA GCAAGCTAGG 450
AAGCGGGCAG CACAGGAGAC AGAACGTCTT CTCAAAGAGT TGGAGCAGAA 500
TGCAAACCAC CCACACCGGA TTGAAATACA GAACATTTTT GAGGAAGCCC 550
AGTCCCTCGT GAGAGAGAAA ATTGTGCCAT TTTATAATGG AGGCAACTGC 600
GTAACTGATG AGTTTGAAGA AGGCATCCAA GATATCATTC TGAGGCTGAC 650
ACATGTTAAA ACTGGAGGAA AAATCTCCTT GCGGAAAGCA AGGTATCACA 700
CTTTAACCAA AATCTGTGCG GTGCAAGAGA TAATCGAAGA CTGCATGAAA 750
AAGCAGCCTT CCCTGCCGCT TTCCGAGGAT GCACATCCTT CCGTTGCCAA 800
AATCAACTTC GTGATGTGTG AGGTGAACAA GGCCCGAGGG GTCCTGATTG 850
CACTTCTGAT GGGTGTGAAC AACAATGAGA CCTGCAGGCA CTTATCCTGT 900
GTGCTCTCGG GGCTGATCGC TGACCTGGAT GCTCTAGATG TGTGCGGCCG 950
GACAGAAATC AGAAATTATC GGAGGGAGGT AGTAGAAGAT ATCAACAAAT 1000
TATTGAAATA TCTGGATTTG GAAGAGGAAG CAGACACAAC TAAAGCATTT 1050
GACCTGAGAC AGAATCATTC CATTTTAAAA ATAGAAAAGG TCCTCAAGAG 1100
AATGAGAGAA ATAAAAAATG AACTTCTCCA AGCACAAAAC CCTTCTGAAT 1150
TGTACCTGAG CTCCAAAACA GAATTGCAGG GTTTAATTGG ACAGTTGGAT 1200
GAGGTAAGTC TTGAAAAAAA CCCCTGCATC CGGGAAGCCA GGAGAAGAGC 1250
AGTGATCGAG GTGCAAACTC TGATCACATA TATTGACTTG AAGGAGGCCC 1300

FIGURE 17A

BNSDOCID <WO 0014106A1 >

FIGURE 17A

TTGAGAAAAG AAAGCTGTTT GCTTGTGAGG AGCACCCATC CCATAAAGCC 1350
GTCTGGAACG TCCTTGGAAA CTTGTCTGAG ATCCAGGGAG AAGTTCTTTC 1400
ATTTGATGGA AATCGAACCG ATAAGAACTA CATCCGGCTG GAAGAGCTGC 1450
TCACCAAGCA GCTGCTAGCC CTGGATGCTG TTGATCCGCA GGGAGAAGAG 1500
AAGTGTAAGG CTGCCAGGAA ACAAGCTGTG AGGCTTGCGC AGAATATTCT 1550
CAGCTATCTC GACCTGAAAT CTGATGAATG GGAGTACTGA AATACCAGAG 1600
ATCTCACTTT TGATACTGTT TTGCACTTCA TATGTGCTTC TATGTATAGA 1650
GAGCTTTCAG TTCATTGATT TATACGTGCA TATTTCAGTC TCAGTATTTA 1700
TGATTGAAGC AAATTCTATT CAGTATCTGC TGCTTTTGAT GTTGCAAGAC 1750
AAATATCATT ACAGCACGTT AACTTTTCCA TTCGGATCAT TATCTGTATG 1800
ATGTGGTGTG GTTTGTTTGG TTTGTCCTTT TTTTTGCGTT TTTAATCAGA 1850
AAACAAAATA GAGGCAGCTT TTGTAGATTT TAAATGGGTT GTGCAAGCAT 1900
TAAAATGCAG GTCTTTCAGA ATCTAGAACT AGGCATAACC TTACATAATA 1950
CTAGGAAAAT TATGAGAAAG GGGAAATTTT TGGTTAAATA AGAGTAAGGT 2000
TCAAACACAA GCAGTACATG TTCTGTTTCA TTATGCTCGA TAGAAGGCTT 2050
TTTTTTCACT TATAAGGCCT GATTGGTCCT ACCCAGCTTA ACGGGGTGGG 2100
GTTTTTTTGT TTGTTCAGAC AGTCTGTTCT TTTGTAAACA TTTTTAGTTG 2150
GAAAAACAGC ATCTGCATTT TCCCCATCCT CTACGTTTTA GAGAGGAATC 2200
TTGTTTTTGT GTGCAACATA AGAAAATTAT GAAAACTAAT AGCCAAAAAA 2250
CCTTTGAGAT TGCATTAAAG AGAAGGGATA AAGGACCAGC AATAATACCT 2300
TGTAAGTTGC TTTTGTTTGT AAAATCTGAG CTTATAGTTT TCCTTAGTGA 2350
GTAAATTCAT AAGGATGGGA ACATTTAAAT TAAGTTAATG GGCCTTTAAA 2400
AAAAAAAAAG GAAACACTCA TACCTGTAGT TGGAGGATGA ATACTGGAGA 2450
CGGGTTACCA ATGTCAGGTT ATACTAAAAC TAAATCAGAA AGTCTGAATG 2500
TAGCACATAA TGGTTCTCTT CTGTTGTCCA AGGCTGTAAA ATGGACAGCC 2550
TTGTCACACC TCCCCGGTGC TGTTTTACAA CGTGAGGGTA GACGCTGTCA 2600

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FIGURE 17A

GTAACCCAGA GGGACCAGGC CTTCCTAGGT TTTCTAGGCA GTCAGCTGTT 2650
AACCACTCAC TTAGTAAATG TCATAACTAC ACCTGCTCCA GGACCAATCA 2700
GTGAAACCTG CTCGGAATTA AAGGCTTCCT CTGGGTGCCT GCTGAACAAC 2750
TGAGCTCATG TCATGGGCAT GTGGTGGTTT CTCTGTTGCC TGAAAGAGCC 2800
ATTAAAGTCA GTCGTGCGTG AAGCATCTCT CTTCTAAAGG ATGTGTATTT 2850
CCATAAATGC TTTCTGAGGA TCCGGTACAA AATGATTTCC CAAAGTTCTG 2900
AAGTGCCTTG AGAACATGTG GGTCCGAGTG TTATAACAGA CTCCTCCCCC 2950
GGGTCACCTT TTGCCTGGTC ATCCTGTTAG AGTACATCTT TGGAAATCCA 3000
GGGTAATATT CTCTTTCAGA GATGCTCATT GTGTAACTCT GTGTAGGGAG 3050
ATAGTCACTT TAAACAGCTC AAAGTAGCTA GCTAAAGGAG TAGCCTTAAA 3100
TACCTAAAAG ATGACAGAAG CATAGCCCTT AACAAATCTT CAGCTTGTCT 3150
CTCAGTATTT CCCAATCATG AAAATCCCTT GCTATGTCTT TCCTACTAGA 3200
AATGTTCTAG AATCGCTGGA CGGTGGGGTC AGAGGGCAGT CGGTATTTAG 3250
GCCGTGAGCT TCCCATACTA CTGCAGGTCC AACTCCTGGC AACCGCGGGC 3300
TCAAGGCAGG TCATTGGAAT CCACGTTTTG GCCACAGTAG TTGTAGGATT 3350
GCTTTTCTGT ATCATAATTT TAGAATGCTC TTAAAATCTT GAGGAAGAGT 3400
TTTTATTTTT TATTTATTTT TGAGATGGAG TCTCTGTTGC CCAGGCTGCA 3450
GTGCAGTGGT GCCATCTCAG CTCACTGCAA CCTCCACCTC CCAGGTTCAA 3500
GCGATTCTCC TGCCTCAGCC ACCTGAGTAG CTGGGAGTAC AGGCATGTGG 3550
CACCATGCCT GGCTAATTTT TGTATTTTTA ATAGAGTTGA GATTTCACCA 3600
TGATGGTCAG GCTGGTCTCG AACTCCTGAC CTCGTGATCC GCCCGCCTCG 3650
GCCCCCCAAA GTGCTGGGAT TAACGGGTGT GAGCCACGGC GCCCAGCCCA 3700
GGAAGAGTTT TTAAATTAGA GCTCTGTTTA ATTATACCAC TGGGAAATCA 3750
TGGTTACGCT TCAGGCATAT TCTTCCCCAG AGTACTACTT ACATTTTAAA 3800
TTTCATTTTG TAAAGTTAAA TGTCAGCATT CCCTTTAAAA GTGTCCATTG 3850
TTCTTTGAAA GTAGACGTTT CAGTCATTCT TTTCAAACAA GTGTTTGTGT 3900

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FIGURE 17A

ACCTTTTGCC AAGCTGTGTGGG CATCGTGTGT GAGTACAGGG TGCTCAGCTC 3950
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TCAGATTGAC CTTGATTGAC TGTCAGGCAT GGCTTTGTTT CTAGTTTCAA 4050
TCTGTTCTCG TTCCTTGTAC CGGATTATTC TACTCCTGCA ATGAACCCTG 4100
TTGACACCGG ATTTAGCTCT TGTCGGCCTT CGTGGGGAGC TGTTTGTGTT 4150
AATATGAGCT ACTGCATGTA ATTCTTAAAC TGGGCTTGTC ACATTGTATT 4200
GTATTTTTGT GATCTGTAAT GAAAAGAATC TGTACTGCAA GTAAAACCTA 4250
CTCCCCAAAA ATGTGTGGCT TTGGGTCTGC ATTAAACGCT GTAGTCCATG 4300
TTCATGCC
4308

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FIGURE 17B

MDMGNQHPSI SRLQEIQKEV KSVEQQVIGF SGLSDDKNYK KLERILTKQL 50
FEIDSVDTEG KGDIQQARKR AAQETERLLK ELEQNANHPH RIEIQNIFEE 100
AQSLVREKIV PFYNGGNCVT DEFEEGIQDI ILRLTHVKTG GKISLRKARY 150
HTLTKICAVQ EIIEDCMKKQ PSLPLSEDAH PSVAKINFVM CEVNKARGVL 200
IALLMGVNNN ETCRHLSCVL SGLIADLDAL DVCGRTEIRN YRREVVEDIN 250
KLLKYLDLEE EADTTKAFDL RQNHSILKIE KVLKRMREIK NELLQAQNPS 300
ELYLSSKTEL QGLIGQLDEV SLEKNPCIRE ARRAVIEVQ TLITYIDLKE 350
ALEKRKLFAC EEHPSHKAVW NVLGNLSEIQ GEVLSFDGNR TDKNYIRLEE 400
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FIGURE 17C

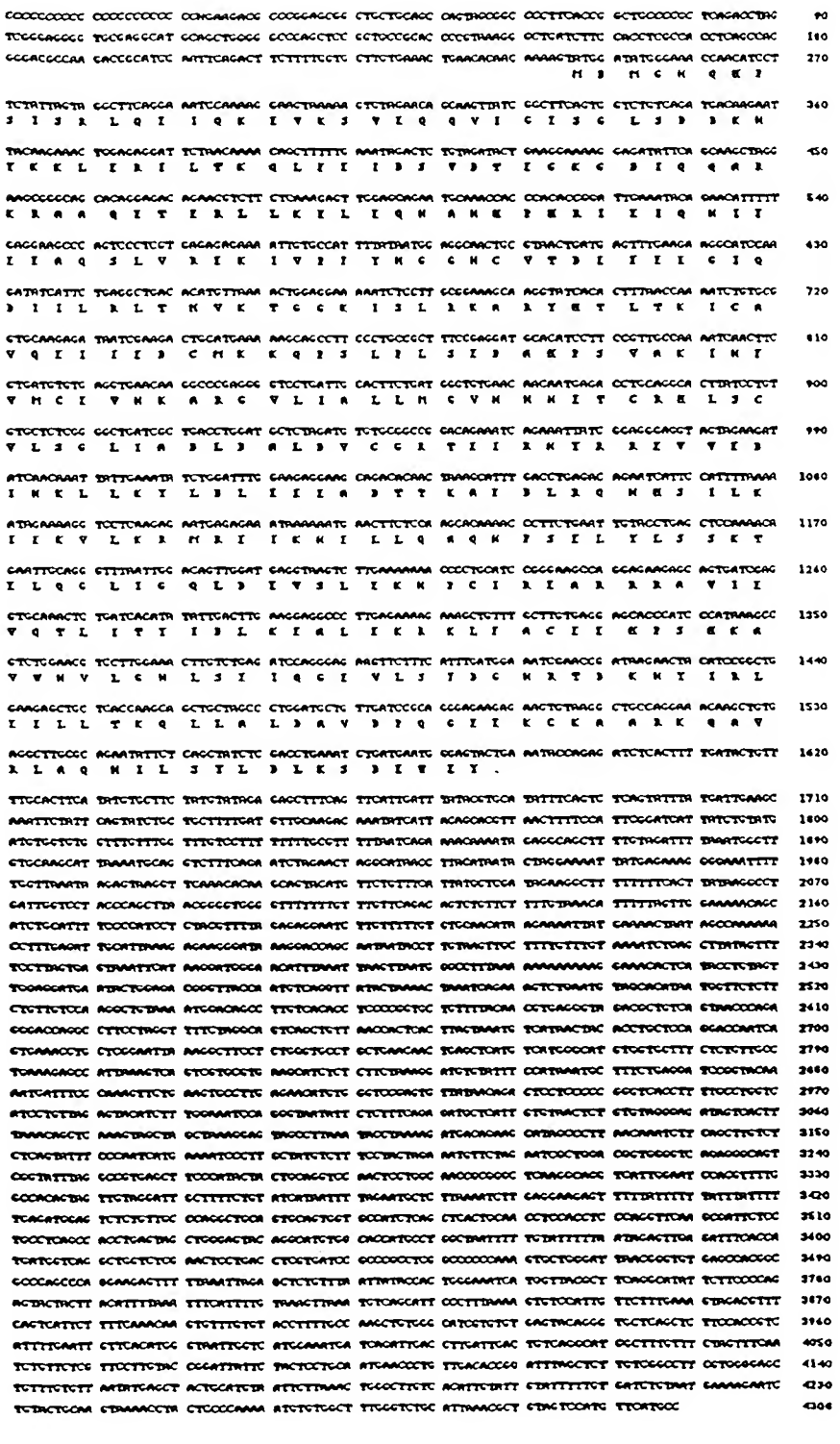
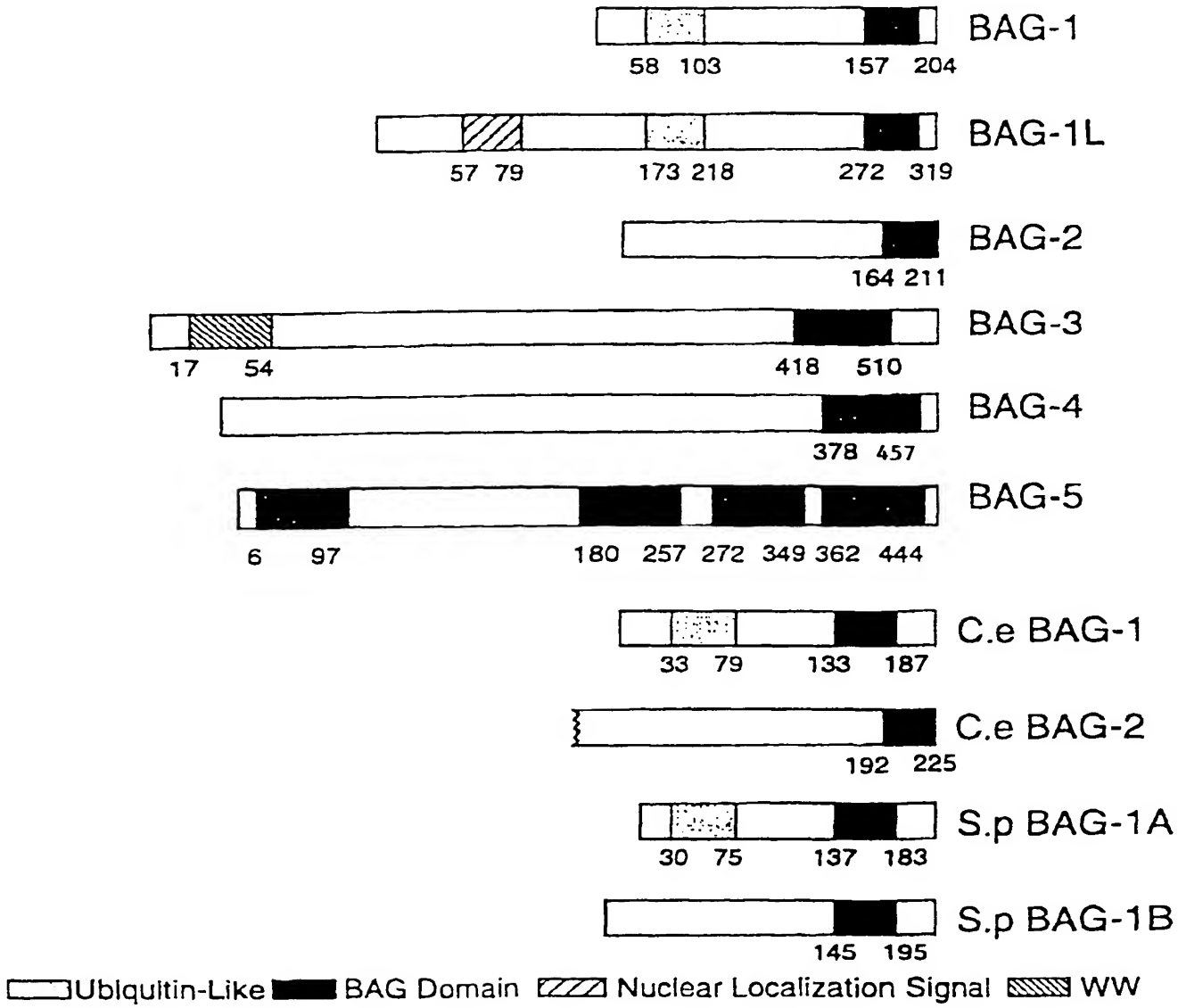


FIGURE 18



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Takayama, Shinichi
The Burnham Institute

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Arg Pro Arg Met Lys Lys Lys Thr Arg Arg Arg Ser Thr Arg Ser Glu
     70                  75                  80

gag ttg acc cgg agc gag gag ttg acc ctg agt gag gaa gcg acc tgg   345
Glu Leu Thr Arg Ser Glu Glu Leu Thr Leu Ser Glu Glu Ala Thr Trp
 85                  90                  95                 100

agt gaa gag gcg acc cag agt gag gag gcg acc cag ggc gaa gag atg   393
Ser Glu Glu Ala Thr Gln Ser Glu Glu Ala Thr Gln Gly Glu Glu Met
                105                 110                 115

aat cgg agc cag gag gtg acc cgg gac gag gag tcg acc cgg agc gag   441
Asn Arg Ser Gln Glu Val Thr Arg Asp Glu Glu Ser Thr Arg Ser Glu
            120                 125                 130

gag gtg acc agg gag gaa atg gcg gca gct ggg ctc acc gtg act gtc   489
Glu Val Thr Arg Glu Glu Met Ala Ala Ala Gly Leu Thr Val Thr Val
        135                 140                 145

acc cac agc aat gag aag cac gac ctt cat gtt acc tcc cag cag ggc   537
Thr His Ser Asn Glu Lys His Asp Leu His Val Thr Ser Gln Gln Gly
    150                 155                 160

agc agt gaa cca gtt gtc caa gac ctg gcc cag gtt gtt gaa gag gtc   585
Ser Ser Glu Pro Val Val Gln Asp Leu Ala Gln Val Val Glu Glu Val
165                 170                 175                 180

ata ggg gtt cca cag tct ttt cag aaa ctc ata ttt aag gga aaa tct   633
Ile Gly Val Pro Gln Ser Phe Gln Lys Leu Ile Phe Lys Gly Lys Ser
                185                 190                 195

ctg aag gaa atg gaa aca ccg ttg tca gca ctt gga ata caa gat ggt   681
Leu Lys Glu Met Glu Thr Pro Leu Ser Ala Leu Gly Ile Gln Asp Gly
            200                 205                 210

tgc cgg gtc atg tta att ggg aaa aag aac agt cca cag gaa gag gtt   729
Cys Arg Val Met Leu Ile Gly Lys Lys Asn Ser Pro Gln Glu Glu Val
        215                 220                 225

gaa cta aag aag ttg aaa cat ttg gag aag tct gtg gag aag ata gct   777
Glu Leu Lys Lys Leu Lys His Leu Glu Lys Ser Val Glu Lys Ile Ala
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Phe Leu Pro Lys Asp Leu Gln Ala Glu Ala Leu Cys Lys Leu Asp Arg
                265                 270                 275

aga gta aaa gcc aca ata gag cag ttt atg aag atc ttg gag gag att   921
Arg Val Lys Ala Thr Ile Glu Gln Phe Met Lys Ile Leu Glu Glu Ile
            280                 285                 290

gac aca ctg atc ctg cca gaa aat ttc aaa gac agt aga ttg aaa agg   969
Asp Thr Leu Ile Leu Pro Glu Asn Phe Lys Asp Ser Arg Leu Lys Arg
        295                 300                 305

aaa ggc ttg gta aaa aag gtt cag gca ttc cta gcc gag tgt gac aca   1017
Lys Gly Leu Val Lys Lys Val Gln Ala Phe Leu Ala Glu Cys Asp Thr
    310                 315                 320

gtg gag cag aac atc tgc cag gag act gag cgg ctg cag tct aca aac   1065
Val Glu Gln Asn Ile Cys Gln Glu Thr Glu Arg Leu Gln Ser Thr Asn
325                 330                 335                 340

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Phe Ala Leu Ala Glu
                345

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Thr Arg Ser Glu Glu Leu Thr Arg Ser Glu Glu Leu Thr Leu Ser Glu
                 85                  90                  95

Glu Ala Thr Trp Ser Glu Glu Ala Thr Gln Ser Glu Glu Ala Thr Gln
            100                 105                 110

Gly Glu Glu Met Asn Arg Ser Gln Glu Val Thr Arg Asp Glu Glu Ser
        115                 120                 125

Thr Arg Ser Glu Glu Val Thr Arg Glu Glu Met Ala Ala Ala Gly Leu
    130                 135                 140

Thr Val Thr Val Thr His Ser Asn Glu Lys His Asp Leu His Val Thr
145                 150                 155                 160

Ser Gln Gln Gly Ser Ser Glu Pro Val Val Gln Asp Leu Ala Gln Val
                165                 170                 175

Val Glu Glu Val Ile Gly Val Pro Gln Ser Phe Gln Lys Leu Ile Phe
            180                 185                 190

Lys Gly Lys Ser Leu Lys Glu Met Glu Thr Pro Leu Ser Ala Leu Gly
        195                 200                 205

Ile Gln Asp Gly Cys Arg Val Met Leu Ile Gly Lys Lys Asn Ser Pro
    210                 215                 220

Gln Glu Glu Val Glu Leu Lys Lys Leu Lys His Leu Glu Lys Ser Val
225                 230                 235                 240

Glu Lys Ile Ala Asp Gln Leu Glu Glu Leu Asn Lys Glu Leu Thr Gly
                245                 250                 255

Ile Gln Gln Gly Phe Leu Pro Lys Asp Leu Gln Ala Glu Ala Leu Cys
            260                 265                 270

Lys Leu Asp Arg Arg Val Lys Ala Thr Ile Glu Gln Phe Met Lys Ile
        275                 280                 285

Leu Glu Glu Ile Asp Thr Leu Ile Leu Pro Glu Asn Phe Lys Asp Ser
    290                 295                 300
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                325                 330                 335

Gln Ser Thr Asn Phe Ala Leu Ala Glu
            340                 345
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ggccggtgac ctcttggcta ccccgcgtcg gaggcttag atg gct cag gcg aag    174
                                          Met Ala Gln Ala Lys
                                            1               5

atc aac gct aaa gcc aac gag ggg cgc ttc tgc cgc tcc tcc tcc atg   222
Ile Asn Ala Lys Ala Asn Glu Gly Arg Phe Cys Arg Ser Ser Ser Met
                10                  15                  20

gct gac cgc tcc agc cgc ctg ctg gag agc ctg gac cag ctg gag ctc   270
Ala Asp Arg Ser Ser Arg Leu Leu Glu Ser Leu Asp Gln Leu Glu Leu
            25                  30                  35

agg gtt gaa gct ttg aga gaa gca gca act gct gtt gag caa gag aaa   318
Arg Val Glu Ala Leu Arg Glu Ala Ala Thr Ala Val Glu Gln Glu Lys
        40                  45                  50

gaa atc ctt ctg gaa atg atc cac agt atc caa aat agc cag gac atg   366
Glu Ile Leu Leu Glu Met Ile His Ser Ile Gln Asn Ser Gln Asp Met
    55                  60                  65

agg cag atc agt gac gga gaa aga gaa gaa tta aat ctg act gca aac   414
Arg Gln Ile Ser Asp Gly Glu Arg Glu Glu Leu Asn Leu Thr Ala Asn
70                  75                  80                  85
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                 90                  95                 100

aga aac ccc cag cag caa gaa tcc cta aag cat gcc aca agg att att   510
Arg Asn Pro Gln Gln Gln Glu Ser Leu Lys His Ala Thr Arg Ile Ile
            105                 110                 115

gat gag gtg gtc aat aag ttt ctg gat gat ttg gga aat gcc aag agt   558
Asp Glu Val Val Asn Lys Phe Leu Asp Asp Leu Gly Asn Ala Lys Ser
        120                 125                 130

cat tta atg tcg ctc tac agt gca tgt tca tct gag gtg cca cat ggg   606
His Leu Met Ser Leu Tyr Ser Ala Cys Ser Ser Glu Val Pro His Gly
    135                 140                 145

cca gtt gat cag aag ttt caa tcc ata gta att ggc tgt gct ctt gaa   654
Pro Val Asp Gln Lys Phe Gln Ser Ile Val Ile Gly Cys Ala Leu Glu
150                 155                 160                 165

gat cag aag aaa att aag aga aga tta gag act ctg ctt aga aat att   702
Asp Gln Lys Lys Ile Lys Arg Arg Leu Glu Thr Leu Leu Arg Asn Ile
                170                 175                 180

gaa aac tct gac aag gcc atc aag cta tta gag cat tct aaa gga gct   750
Glu Asn Ser Asp Lys Ala Ile Lys Leu Leu Glu His Ser Lys Gly Ala
            185                 190                 195

ggt tcc aaa act ctg caa caa aat gct gaa agc aga ttc aat           798
Gly Ser Lys Thr Leu Gln Gln Asn Ala Glu Ser Arg Phe Asn
        200                 205                 210

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attttaatta tctatctaga gatttttag attgaattct tgtcttgtac taggatctag 1038

catatttcac tattctgtgg atgaatacat agtttgtggg gaaaacaaac gttcagctag 1098

gggcaaaaag catgactgct ttttcctgtc tggcatggaa tcacgcagtc accttgggca 1158

tttagtttac tagaaattct ttactgg                                    1179
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BNSDOCID <WO 0014106A1 | >

<210> 4
<211> 211
<212> PRT
<213> Homo sapiens

<400> 4

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Met Ala Gln Ala Lys Ile Asn Ala Lys Ala Asn Glu Gly Arg Phe Cys
  1               5                  10                  15

Arg Ser Ser Ser Met Ala Asp Arg Ser Ser Arg Leu Leu Glu Ser Leu
            20                  25                  30

Asp Gln Leu Glu Leu Arg Val Glu Ala Leu Arg Glu Ala Ala Thr Ala
        35                  40                  45

Val Glu Gln Glu Lys Glu Ile Leu Leu Glu Met Ile His Ser Ile Gln
    50                  55                  60

Asn Ser Gln Asp Met Arg Gln Ile Ser Asp Gly Glu Arg Glu Glu Leu
65                  70                  75                  80

Asn Leu Thr Ala Asn Arg Leu Met Gly Arg Thr Leu Thr Val Glu Val
                85                  90                  95

Ser Val Glu Thr Ile Arg Asn Pro Gln Gln Gln Glu Ser Leu Lys His
            100                 105                 110

Ala Thr Arg Ile Ile Asp Glu Val Val Asn Lys Phe Leu Asp Asp Leu
        115                 120                 125

Gly Asn Ala Lys Ser His Leu Met Ser Leu Tyr Ser Ala Cys Ser Ser
    130                 135                 140

Glu Val Pro His Gly Pro Val Asp Gln Lys Phe Gln Ser Ile Val Ile
145                 150                 155                 160

Gly Cys Ala Leu Glu Asp Gln Lys Lys Ile Lys Arg Arg Leu Glu Thr
                165                 170                 175

Leu Leu Arg Asn Ile Glu Asn Ser Asp Lys Ala Ile Lys Leu Leu Glu
            180                 185                 190

His Ser Lys Gly Ala Gly Ser Lys Thr Leu Gln Gln Asn Ala Glu Ser
        195                 200                 205

Arg Phe Asn
    210
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BNSDOCID <WO 0014106A1 >

<210> 5
<211> 2528
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(2031)

<400> 5

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gcg gag ctc cgc atc caa ccc cgg gcc gcg gcc aac ttc tct gga ctg   48
Ala Glu Leu Arg Ile Gln Pro Arg Ala Ala Ala Asn Phe Ser Gly Leu
  1               5                  10                  15

gac cag aag ttt cta gcc ggc cag ttg cta cct ccc ttt atc tcc tcc   96
Asp Gln Lys Phe Leu Ala Gly Gln Leu Leu Pro Pro Phe Ile Ser Ser
             20                  25                  30

ttc ccc tct ggc agc gag gag gct att tcc aga cac ttc cac ccc tct   144
Phe Pro Ser Gly Ser Glu Glu Ala Ile Ser Arg His Phe His Pro Ser
         35                  40                  45

ctg gcc acg tca ccc ccg cct tta att cat aaa ggt gcc cgg cgc cgg   192
Leu Ala Thr Ser Pro Pro Pro Leu Ile His Lys Gly Ala Arg Arg Arg
     50                  55                  60

ctt ccc gga cac gtc ggc ggc gga gag ggg ccc acg gcg gcg gcc cgg   240
Leu Pro Gly His Val Gly Gly Gly Glu Gly Pro Thr Ala Ala Ala Arg
 65                  70                  75                  80

cca gag act cgg cgc ccg gag cca gcg ccc cgc acc cgc gcc cca gcg   288
Pro Glu Thr Arg Arg Pro Glu Pro Ala Pro Arg Thr Arg Ala Pro Ala
                 85                  90                  95

ggc aga ccc caa ccc agc atg agc gcc gcc acc cac tcg ccc atg atg   336
Gly Arg Pro Gln Pro Ser Met Ser Ala Ala Thr His Ser Pro Met Met
            100                 105                 110

cag gtg gcg tcc ggc aac ggt gac cgc gac cct ttg ccc ccc gga tgg   384
Gln Val Ala Ser Gly Asn Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp
        115                 120                 125

gag atc aag atc gac ccg cag acc ggc tgg ccc ttc ttc gtg gac cac   432
Glu Ile Lys Ile Asp Pro Gln Thr Gly Trp Pro Phe Phe Val Asp His
    130                 135                 140

aac agc cgc acc act acg tgg aac gac ccg cgc gtg ccc tct gag ggc   480
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BNSDOCID <WO 0014106A1 I >

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Asn Ser Arg Thr Thr Thr Trp Asn Asp Pro Arg Val Pro Ser Glu Gly
145                 150                 155                 160

ccc aag gag act cca tcc tct gcc aat ggc cct tcc cgg gag ggc tct   528
Pro Lys Glu Thr Pro Ser Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser
                165                 170                 175

agg ctg ccg cct gct agg gaa ggc cac cct gtg tac ccc cag ctc cga   576
Arg Leu Pro Pro Ala Arg Glu Gly His Pro Val Tyr Pro Gln Leu Arg
            180                 185                 190

cca ggc tac att ccc att cct gtg ctc cat gaa ggc gct gag aac cgg   624
Pro Gly Tyr Ile Pro Ile Pro Val Leu His Glu Gly Ala Glu Asn Arg
        195                 200                 205

cag gtg cac cct ttc cat gtc tat ccc cag cct ggg atg cag cga ttc   672
Gln Val His Pro Phe His Val Tyr Pro Gln Pro Gly Met Gln Arg Phe
    210                 215                 220

cga act gag gcg gca gca gcg gct cct cag agg tcc cag tca cct ctg   720
Arg Thr Glu Ala Ala Ala Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu
225                 230                 235                 240

cgg ggc atg cca gaa acc act cag cca gat aaa cag tgt gga cag gtg   768
Arg Gly Met Pro Glu Thr Thr Gln Pro Asp Lys Gln Cys Gly Gln Val
                245                 250                 255

gca gcg gcg gcg gca gcc cag ccc cca gcc tcc cac gga cct gag cgg   816
Ala Ala Ala Ala Ala Ala Gln Pro Pro Ala Ser His Gly Pro Glu Arg
            260                 265                 270

tcc cag tct cca gct gcc tct gac tgc tca tcc tca tcc tcc tcg gcc   864
Ser Gln Ser Pro Ala Ala Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala
        275                 280                 285

agc ctg cct tcc tcc ggc agg agc agc ctg ggc agt cac cag ctc ccg   912
Ser Leu Pro Ser Ser Gly Arg Ser Ser Leu Gly Ser His Gln Leu Pro
    290                 295                 300

cgg ggg tac atc tcc att ccg gtg ata cac gag cag aac gtt acc cgg   960
Arg Gly Tyr Ile Ser Ile Pro Val Ile His Glu Gln Asn Val Thr Arg
305                 310                 315                 320

cca gca gcc cag ccc tcc ttc cac aaa gcc cag aag acg cac tac cca  1008
Pro Ala Ala Gln Pro Ser Phe His Lys Ala Gln Lys Thr His Tyr Pro
                325                 330                 335

gcg cag agg ggt gag tac cag acc cac cag cct gtg tac cac aag atc  1056
```


BNSDOCID: <WO 0014106A1 >

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Ala Gln Arg Gly Glu Tyr Gln Thr His Gln Pro Val Tyr His Lys Ile
            340                 345                 350

cag ggg gat gac tgg gag ccc cgg ccc ctg cgg gcg gca tcc ccg ttc   1104
Gln Gly Asp Asp Trp Glu Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe
        355                 360                 365

agg tca tct gtc cag ggt gca tcg agc cgg gag ggc tca cca gcc agg   1152
Arg Ser Ser Val Gln Gly Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg
    370                 375                 380

agc agc acg cca ctc cac tcc ccc tcg ccc atc cgt gtg cac acc gtg   1200
Ser Ser Thr Pro Leu His Ser Pro Ser Pro Ile Arg Val His Thr Val
385                 390                 395                 400

gtc gac agg cct cag cag ccc atg acc cat cga gaa act gca cct gtt   1248
Val Asp Arg Pro Gln Gln Pro Met Thr His Arg Glu Thr Ala Pro Val
                405                 410                 415

tcc cag cct gaa aac aaa cca gaa agt aag cca ggc cca gtt gga cca   1296
Ser Gln Pro Glu Asn Lys Pro Glu Ser Lys Pro Gly Pro Val Gly Pro
            420                 425                 430

gaa ctc cct cct gga cac atc cca att caa gtg atc cgc aaa gag gtg   1344
Glu Leu Pro Pro Gly His Ile Pro Ile Gln Val Ile Arg Lys Glu Val
        435                 440                 445

gat tct aaa cct gtt tcc cag aag ccc cca cct ccc tct gag aag gta   1392
Asp Ser Lys Pro Val Ser Gln Lys Pro Pro Pro Pro Ser Glu Lys Val
    450                 455                 460

gag gtg aaa gtt ccc cct gct cca gtt cct tgt cct cct ccc agc cct   1440
Glu Val Lys Val Pro Pro Ala Pro Val Pro Cys Pro Pro Pro Ser Pro
465                 470                 475                 480

ggc cct tct gct gtc ccc tct tcc ccc aag agt gtg gct aca gaa gag   1488
Gly Pro Ser Ala Val Pro Ser Ser Pro Lys Ser Val Ala Thr Glu Glu
                485                 490                 495

agg gca gcc ccc agc act gcc cct gca gaa gct aca cct cca aaa cca   1536
Arg Ala Ala Pro Ser Thr Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro
            500                 505                 510

gga gaa gcc gag gct ccc cca aaa cat cca gga gtg ctg aaa gtg gaa   1584
Gly Glu Ala Glu Ala Pro Pro Lys His Pro Gly Val Leu Lys Val Glu
        515                 520                 525

gcc atc ctg gag aag gtg cag ggg ctg gag cag gct gta gac aac ttt   1632
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BNSDOCID <WO __0014106A1_I_>

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Ala Ile Leu Glu Lys Val Gln Gly Leu Glu Gln Ala Val Asp Asn Phe
    530                 535                 540

gaa ggc aag aag act gac aaa aag tac ctg atg atc gaa gag tat ttg   1680
Glu Gly Lys Lys Thr Asp Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu
545                 550                 555                 560

acc aaa gag ctg ctg gcc ctg gat tca gtg gac ccc gag gga cga gcc   1728
Thr Lys Glu Leu Leu Ala Leu Asp Ser Val Asp Pro Glu Gly Arg Ala
                565                 570                 575

gat gtg cgt cag gcc agg aga gac ggt gtc agg aag gtt cag acc atc   1776
Asp Val Arg Gln Ala Arg Arg Asp Gly Val Arg Lys Val Gln Thr Ile
            580                 585                 590

ttg gaa aaa ctt gaa cag aaa gcc att gat gtc cca ggt caa gtc cag   1824
Leu Glu Lys Leu Glu Gln Lys Ala Ile Asp Val Pro Gly Gln Val Gln
        595                 600                 605

gtc tat gaa ctc cag ccc agc aac ctt gaa gca gat cag cca ctg cag   1872
Val Tyr Glu Leu Gln Pro Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln
    610                 615                 620

gca atc atg gag atg ggt gcc gtg gca gca gac aag ggc aag aaa aat   1920
Ala Ile Met Glu Met Gly Ala Val Ala Ala Asp Lys Gly Lys Lys Asn
625                 630                 635                 640

gct gga aat gca gaa gat ccc cac aca gaa acc cag cag cca gaa gcc   1968
Ala Gly Asn Ala Glu Asp Pro His Thr Glu Thr Gln Gln Pro Glu Ala
                645                 650                 655

aca gca gca gcg act tca aac ccc agc agc atg aca gac acc cct ggt   2016
Thr Ala Ala Ala Thr Ser Asn Pro Ser Ser Met Thr Asp Thr Pro Gly
            660                 665                 670

aac cca gca gca ccg tagcctctgc cctgtaaaag tcagactcgg aaccgatgtg   2071
Asn Pro Ala Ala Pro
        675

tgctttaggg attttagttg catgcatttc agagacttta ggtcagttgg ttttgattag 2131

ctgcttggta tgcagtactt gggtgaggca aacactataa agggctaaaa gggaaaatga 2191

tgcttttctt caatattctt actcttgtac aattaangaa gttgcttgtt gtttgagaag 2251

tttaaccccg ttgcttgttc tgcagccctg tcnacttggg caccccccacc acctgttagc 2311

tgtggttgtg cactgtcttt tgtagctctg gactggaggg gtagatgggg agtcaattac 2371
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BNSDOCID <WO 0014106A1 | >

ccatcacata aatatgaaac atttatcaga aatgttgcca ttttaatgag atgattttct 2431

tcatctcata attaaaatac ctgactttag agagagtaaa atgtgccagg agccatagga 2491

atatctgtat gttggatgac tttaatgcta catttth 2528

<210> 6
<211> 677
<212> PRT
<213> Homo sapiens

<400> 6

Ala Glu Leu Arg Ile Gln Pro Arg Ala Ala Ala Asn Phe Ser Gly Leu
1 5 10 15

Asp Gln Lys Phe Leu Ala Gly Gln Leu Leu Pro Pro Phe Ile Ser Ser
20 25 30

Phe Pro Ser Gly Ser Glu Glu Ala Ile Ser Arg His Phe His Pro Ser
35 40 45

Leu Ala Thr Ser Pro Pro Pro Leu Ile His Lys Gly Ala Arg Arg Arg
50 55 60

Leu Pro Gly His Val Gly Gly Gly Glu Gly Pro Thr Ala Ala Ala Arg
65 70 75 80

Pro Glu Thr Arg Arg Pro Glu Pro Ala Pro Arg Thr Arg Ala Pro Ala
85 90 95

Gly Arg Pro Gln Pro Ser Met Ser Ala Ala Thr His Ser Pro Met Met
100 105 110

Gln Val Ala Ser Gly Asn Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp
115 120 125

Glu Ile Lys Ile Asp Pro Gln Thr Gly Trp Pro Phe Phe Val Asp His
130 135 140

Asn Ser Arg Thr Thr Thr Trp Asn Asp Pro Arg Val Pro Ser Glu Gly
145 150 155 160

Pro Lys Glu Thr Pro Ser Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser
165 170 175

Arg Leu Pro Pro Ala Arg Glu Gly His Pro Val Tyr Pro Gln Leu Arg

BNSDOCID <WO 0014106A1_I_>

180 185 190

Pro Gly Tyr Ile Pro Ile Pro Val Leu His Glu Gly Ala Glu Asn Arg
195 200 205

Gln Val His Pro Phe His Val Tyr Pro Gln Pro Gly Met Gln Arg Phe
210 215 220

Arg Thr Glu Ala Ala Ala Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu
225 230 235 240

Arg Gly Met Pro Glu Thr Thr Gln Pro Asp Lys Gln Cys Gly Gln Val
245 250 255

Ala Ala Ala Ala Ala Ala Gln Pro Pro Ala Ser His Gly Pro Glu Arg
260 265 270

Ser Gln Ser Pro Ala Ala Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala
275 280 285

Ser Leu Pro Ser Ser Gly Arg Ser Ser Leu Gly Ser His Gln Leu Pro
290 295 300

Arg Gly Tyr Ile Ser Ile Pro Val Ile His Glu Gln Asn Val Thr Arg
305 310 315 320

Pro Ala Ala Gln Pro Ser Phe His Lys Ala Gln Lys Thr His Tyr Pro
325 330 335

Ala Gln Arg Gly Glu Tyr Gln Thr His Gln Pro Val Tyr His Lys Ile
340 345 350

Gln Gly Asp Asp Trp Glu Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe
355 360 365

Arg Ser Ser Val Gln Gly Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg
370 375 380

Ser Ser Thr Pro Leu His Ser Pro Ser Pro Ile Arg Val His Thr Val
385 390 395 400

Val Asp Arg Pro Gln Gln Pro Met Thr His Arg Glu Thr Ala Pro Val
405 410 415

Ser Gln Pro Glu Asn Lys Pro Glu Ser Lys Pro Gly Pro Val Gly Pro
420 425 430

Glu Leu Pro Pro Gly His Ile Pro Ile Gln Val Ile Arg Lys Glu Val

BNSDOCID: <WO 0014106A1 I >

435 440 445

Asp Ser Lys Pro Val Ser Gln Lys Pro Pro Pro Pro Ser Glu Lys Val
450 455 460

Glu Val Lys Val Pro Pro Ala Pro Val Pro Cys Pro Pro Pro Ser Pro
465 470 475 480

Gly Pro Ser Ala Val Pro Ser Ser Pro Lys Ser Val Ala Thr Glu Glu
485 490 495

Arg Ala Ala Pro Ser Thr Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro
500 505 510

Gly Glu Ala Glu Ala Pro Pro Lys His Pro Gly Val Leu Lys Val Glu
515 520 525

Ala Ile Leu Glu Lys Val Gln Gly Leu Glu Gln Ala Val Asp Asn Phe
530 535 540

Glu Gly Lys Lys Thr Asp Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu
545 550 555 560

Thr Lys Glu Leu Leu Ala Leu Asp Ser Val Asp Pro Glu Gly Arg Ala
565 570 575

Asp Val Arg Gln Ala Arg Arg Asp Gly Val Arg Lys Val Gln Thr Ile
580 585 590

Leu Glu Lys Leu Glu Gln Lys Ala Ile Asp Val Pro Gly Gln Val Gln
595 600 605

Val Tyr Glu Leu Gln Pro Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln
610 615 620

Ala Ile Met Glu Met Gly Ala Val Ala Ala Asp Lys Gly Lys Lys Asn
625 630 635 640

Ala Gly Asn Ala Glu Asp Pro His Thr Glu Thr Gln Gln Pro Glu Ala
645 650 655

Thr Ala Ala Ala Thr Ser Asn Pro Ser Ser Met Thr Asp Thr Pro Gly
660 665 670

Asn Pro Ala Ala Pro
675

BNSDOCID <WO 0014106A1 I_>

<210> 7
<211> 1010
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (323)..(1009)

<400> 7
acgatatcct gtaagaccaa gaattgcaag gccagagttt gaattcttat acaaatggag 60

cgtatggtcc aacatacccc ccaggccctg gggcaaatac tgcctcatac tcaggggctt 120

attatgcacc tggttatact cagaccagtt actccacaga agttccaagt acttaccgtt 180

catctggcaa cagcccaact ccagtctctc gttggatcta tccccagcag gactgtcaag 240

actgaagcac cccctcttaa ggggcaggtt ccaggatatc cgccttcaca gaaccctgga 300

atgaccctgc cccattatcc tt atg gag atg gta atc gta gtg ttc cac aat 352
Met Glu Met Val Ile Val Val Phe His Asn
1 5 10

cac ggc cga ctg tac gac cac aag aaa gat gcg tgg gct tct cct ggt 400
His Gly Arg Leu Tyr Asp His Lys Lys Asp Ala Trp Ala Ser Pro Gly
15 20 25

gct tat gga atg ggt ggc cgt tat ccc tgg cct tca tca gcg ccc tca 448
Ala Tyr Gly Met Gly Gly Arg Tyr Pro Trp Pro Ser Ser Ala Pro Ser
30 35 40

gca cca ccc ggc aat ctc tac atg act gaa agt act tca cca tgg cct 496
Ala Pro Pro Gly Asn Leu Tyr Met Thr Glu Ser Thr Ser Pro Trp Pro
45 50 55

agc agt ggc tct ccc cag tca ccc cct tca ccc cca gtc cag cag ccc 544
Ser Ser Gly Ser Pro Gln Ser Pro Pro Ser Pro Pro Val Gln Gln Pro
60 65 70

aag gat tct tca tac ccc tat agc caa tca gat caa agc atg aac cgg 592
Lys Asp Ser Ser Tyr Pro Tyr Ser Gln Ser Asp Gln Ser Met Asn Arg
75 80 85 90

cac aac ttt cct tgc agt gtc cat cag tac gaa tcc tcg ggg aca gtg 640
His Asn Phe Pro Cys Ser Val His Gln Tyr Glu Ser Ser Gly Thr Val
95 100 105

BNSDOCID <WO 0014106A1 >

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aac aat gat gat tca gat ctt ttg gat tcc caa gtc cag tat agt gct   688
Asn Asn Asp Asp Ser Asp Leu Leu Asp Ser Gln Val Gln Tyr Ser Ala
            110                 115                 120

gag cct cag ctg tat ggt aat gcc acc agt gac cat ccc aac aat caa   736
Glu Pro Gln Leu Tyr Gly Asn Ala Thr Ser Asp His Pro Asn Asn Gln
        125                 130                 135

gat caa agt agc agt ctt cct gaa gaa tgt gta cct tca gat gaa agt   784
Asp Gln Ser Ser Ser Leu Pro Glu Glu Cys Val Pro Ser Asp Glu Ser
    140                 145                 150

act cct ccg agt att aaa aaa atc ata cat gtg ctg gag aag gtc cag   832
Thr Pro Pro Ser Ile Lys Lys Ile Ile His Val Leu Glu Lys Val Gln
155                 160                 165                 170

tat ctt gaa caa gaa gta gaa gaa ttt gta gga aaa aag aca gac aaa   880
Tyr Leu Glu Gln Glu Val Glu Glu Phe Val Gly Lys Lys Thr Asp Lys
                175                 180                 185

gca tac tgg ctt ctg gaa gaa atg cta acc aag gaa ctt ttg gaa ctg   928
Ala Tyr Trp Leu Leu Glu Glu Met Leu Thr Lys Glu Leu Leu Glu Leu
            190                 195                 200

gat tca gtt gaa act ggg ggc cag gac tct gta cgg cag gcc aga aaa   976
Asp Ser Val Glu Thr Gly Gly Gln Asp Ser Val Arg Gln Ala Arg Lys
        205                 210                 215

gag gct gtt tgt aag att cag gcc ata ttg gaa a                    1010
Glu Ala Val Cys Lys Ile Gln Ala Ile Leu Glu
    220                 225
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<210> 8
<211> 229
<212> PRT
<213> Homo sapiens

<400> 8

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Met Glu Met Val Ile Val Val Phe His Asn His Gly Arg Leu Tyr Asp
  1               5                  10                  15

His Lys Lys Asp Ala Trp Ala Ser Pro Gly Ala Tyr Gly Met Gly Gly
             20                  25                  30

Arg Tyr Pro Trp Pro Ser Ser Ala Pro Ser Ala Pro Pro Gly Asn Leu
         35                  40                  45
```


BNSDOCID <WO 0014106A1 >

```
Tyr Met Thr Glu Ser Thr Ser Pro Trp Pro Ser Ser Gly Ser Pro Gln
     50                  55                  60

Ser Pro Pro Ser Pro Pro Val Gln Gln Pro Lys Asp Ser Ser Tyr Pro
 65                  70                  75                  80

Tyr Ser Gln Ser Asp Gln Ser Met Asn Arg His Asn Phe Pro Cys Ser
                 85                  90                  95

Val His Gln Tyr Glu Ser Ser Gly Thr Val Asn Asn Asp Asp Ser Asp
            100                 105                 110

Leu Leu Asp Ser Gln Val Gln Tyr Ser Ala Glu Pro Gln Leu Tyr Gly
        115                 120                 125

Asn Ala Thr Ser Asp His Pro Asn Asn Gln Asp Gln Ser Ser Ser Leu
    130                 135                 140

Pro Glu Glu Cys Val Pro Ser Asp Glu Ser Thr Pro Pro Ser Ile Lys
145                 150                 155                 160

Lys Ile Ile His Val Leu Glu Lys Val Gln Tyr Leu Glu Gln Glu Val
                165                 170                 175

Glu Glu Phe Val Gly Lys Lys Thr Asp Lys Ala Tyr Trp Leu Leu Glu
            180                 185                 190

Glu Met Leu Thr Lys Glu Leu Leu Glu Leu Asp Ser Val Glu Thr Gly
        195                 200                 205

Gly Gln Asp Ser Val Arg Gln Ala Arg Lys Glu Ala Val Cys Lys Ile
    210                 215                 220

Gln Ala Ile Leu Glu
225
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<210> 9
<211> 689
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (3)..(482)

<220>
<221> unsure

BNSDOCID <WO 0014106A1 | >

<222> (105)
<223> any amino acid

<400> 9

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ga gaa ata aaa aat gaa ctt ctc caa gca caa aac cct tct gaa ttg    47
   Glu Ile Lys Asn Glu Leu Leu Gln Ala Gln Asn Pro Ser Glu Leu
     1               5                  10                  15

tac ctg agc tcc aaa aca gaa ttg cag ggt tta att gga cag ttg gat   95
Tyr Leu Ser Ser Lys Thr Glu Leu Gln Gly Leu Ile Gly Gln Leu Asp
                 20                  25                  30

gag gta agt ntt gaa aaa aac ccc tgc atc cgg gaa gcc agg aga aga   143
Glu Val Ser Xaa Glu Lys Asn Pro Cys Ile Arg Glu Ala Arg Arg Arg
             35                  40                  45

gca gtg atc gag gtg caa act ctg atc aca tat att gac ttg aag gag   191
Ala Val Ile Glu Val Gln Thr Leu Ile Thr Tyr Ile Asp Leu Lys Glu
         50                  55                  60

gcc ctt gag aaa aga aag ctg ttt gct tgt gag gag cac cca tcc cat   239
Ala Leu Glu Lys Arg Lys Leu Phe Ala Cys Glu Glu His Pro Ser His
     65                  70                  75

aaa gcc gtc tgg aac gtc ctt gga aac ttg tct gag atc cag gga gaa   287
Lys Ala Val Trp Asn Val Leu Gly Asn Leu Ser Glu Ile Gln Gly Glu
 80                  85                  90                  95

gtt ctt tca ttt gat gga aat cga acc gat aag aac tac atc cgg ctg   335
Val Leu Ser Phe Asp Gly Asn Arg Thr Asp Lys Asn Tyr Ile Arg Leu
                100                 105                 110

gaa gag ctg ctc acc aag cag ctg cta gcc ctg gat gct gtt gat ccg   383
Glu Glu Leu Leu Thr Lys Gln Leu Leu Ala Leu Asp Ala Val Asp Pro
            115                 120                 125

cag gga gaa gag aag tgt aag gct gcc agg aaa caa gct gtg agg ctt   431
Gln Gly Glu Glu Lys Cys Lys Ala Ala Arg Lys Gln Ala Val Arg Leu
        130                 135                 140

gcg cag aat att ctc agc tat ctc gac ctg aaa tct gat gaa tgg gag   479
Ala Gln Asn Ile Leu Ser Tyr Leu Asp Leu Lys Ser Asp Glu Trp Glu
    145                 150                 155

tac tgaaatacca gagatctcac ttttgatact gttttgcact tcatatgtgc        532
Tyr
160
```


BNSDOCID <WO 0014106A1 I_>

ttctatgtat agagagcttt cagttcattg atttatacgt gcatatttca gtctcagtat 592

ttatgattga agcaaattct attcagtatc tgctgctttt gatgttgcaa gacaaatatc 652

attacagcac gttaactttt ccattcggat caaaaaa 689

<210> 10
<211> 160
<212> PRT
<213> Homo sapiens

<400> 10

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Glu Ile Lys Asn Glu Leu Leu Gln Ala Gln Asn Pro Ser Glu Leu Tyr
  1               5                  10                  15

Leu Ser Ser Lys Thr Glu Leu Gln Gly Leu Ile Gly Gln Leu Asp Glu
             20                  25                  30

Val Ser Xaa Glu Lys Asn Pro Cys Ile Arg Glu Ala Arg Arg Arg Ala
         35                  40                  45

Val Ile Glu Val Gln Thr Leu Ile Thr Tyr Ile Asp Leu Lys Glu Ala
     50                  55                  60

Leu Glu Lys Arg Lys Leu Phe Ala Cys Glu Glu His Pro Ser His Lys
 65                  70                  75                  80

Ala Val Trp Asn Val Leu Gly Asn Leu Ser Glu Ile Gln Gly Glu Val
                 85                  90                  95

Leu Ser Phe Asp Gly Asn Arg Thr Asp Lys Asn Tyr Ile Arg Leu Glu
            100                 105                 110

Glu Leu Leu Thr Lys Gln Leu Leu Ala Leu Asp Ala Val Asp Pro Gln
        115                 120                 125

Gly Glu Glu Lys Cys Lys Ala Ala Arg Lys Gln Ala Val Arg Leu Ala
    130                 135                 140

Gln Asn Ile Leu Ser Tyr Leu Asp Leu Lys Ser Asp Glu Trp Glu Tyr
145                 150                 155                 160
```

<210> 11
<211> 246
<212> DNA
<213> Caenorhabditis elegans

BNSDOCID <WO 0014106A1 | >

<400> 11
atgtctttcc gcctcttcgt tgaaatattt cactttcttt tccagctttt tccccatctc 60

gacctgcttt ggtttttcga gaaaaccacg ttccaaatca gcgacatctc tcaaattgag 120

atcataggct ttttgaagat tgctcaaatt atgcttctca tattgcatga gcattttgaa 180

gcccgcgtca tcaaccaaag catttttttcc acccatcaca atgattttat catttctttt 240

aaaatt 246

<210> 12
<211> 210
<212> PRT
<213> Caenorhabditis elegans

<400> 12
Met Lys Val Asn Val Ser Cys Ser Ser Val Gln Thr Thr Ile Asp Ile
1 5 10 15

Leu Glu Glu Asn Gln Gly Glu Asp Glu Ser Ile Leu Thr Leu Gly Gln
20 25 30

Leu Arg Asp Arg Ile Ala Thr Asp Asn Asp Val Asp Val Glu Thr Met
35 40 45

Lys Leu Leu His Arg Gly Lys Phe Leu Gln Gly Ala Asp Asp Val Ser
50 55 60

Leu Ser Thr Leu Asn Phe Lys Glu Asn Asp Lys Ile Ile Val Met Gly
65 70 75 80

Gly Lys Asn Ala Leu Val Asp Asp Ala Gly Phe Lys Met Leu Met Gln
85 90 95

Tyr Glu Lys His Asn Leu Ser Asn Leu Gln Lys Ala Tyr Asp Leu Asn
100 105 110

Leu Arg Asp Val Ala Asp Leu Glu Arg Gly Phe Leu Glu Lys Pro Lys
115 120 125

Gln Val Glu Met Gly Lys Lys Leu Glu Lys Lys Val Lys Tyr Phe Asn
130 135 140

Glu Glu Ala Glu Arg His Leu Glu Thr Leu Asp Gly Met Asn Ile Ile
145 150 155 160

BNSDOCID <WO 0014106A1 >

```
Thr Glu Thr Thr Pro Glu Asn Gln Ala Lys Arg Asn Arg Glu Lys Arg
                165                 170                 175

Lys Thr Leu Val Asn Gly Ile Gln Thr Leu Leu Asn Gln Asn Asp Ala
            180                 185                 190

Leu Leu Arg Arg Leu Gln Glu Tyr Gln Ser Val Leu Asn Gly Asp Ile
        195                 200                 205

Pro Glu
    210
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<210> 13
<211> 1377
<212> DNA
<213> Caenorhabditis elegans

<220>
<221> CDS
<222> (1)..(1377)

<400> 13

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atg cca gtc gtg aac ata cca atc aaa ata ctt ggt cag aat caa tca   48
Met Pro Val Val Asn Ile Pro Ile Lys Ile Leu Gly Gln Asn Gln Ser
  1               5                  10                  15

cat agt cga agt aac tcc tcg tct tct gtt gac aac gat cga aat caa   96
His Ser Arg Ser Asn Ser Ser Ser Ser Val Asp Asn Asp Arg Asn Gln
            20                  25                  30

cca cca cag cag cca cct caa ccg caa cca caa cag caa tct cag caa   144
Pro Pro Gln Gln Pro Pro Gln Pro Gln Pro Gln Gln Gln Ser Gln Gln
        35                  40                  45

caa tac cag cag gct cca aac gtg aat acc aat atg cat cat tcc aac   192
Gln Tyr Gln Gln Ala Pro Asn Val Asn Thr Asn Met His His Ser Asn
    50                  55                  60

gga ttc tca cct aac ttc cca tct cgt agt cct att ccg gac ttt ccc   240
Gly Phe Ser Pro Asn Phe Pro Ser Arg Ser Pro Ile Pro Asp Phe Pro
65                  70                  75                  80

agt ttt tca tct ggg ttc cca aac gat tct gaa tgg tct tcg aat ttc   288
Ser Phe Ser Ser Gly Phe Pro Asn Asp Ser Glu Trp Ser Ser Asn Phe
                85                  90                  95
```


BNSDOCID <WO 0014106A1 | >

```
ccg tcg ttt cca aat ttc cca agt gga ttc tca aat gga agt tct aat   336
Pro Ser Phe Pro Asn Phe Pro Ser Gly Phe Ser Asn Gly Ser Ser Asn
            100                 105                 110

ttc cct gat ttt cca aga ttc gga aga gat gga gga cta tcg cca aac   384
Phe Pro Asp Phe Pro Arg Phe Gly Arg Asp Gly Gly Leu Ser Pro Asn
        115                 120                 125

cca ccg atg caa gga tac agg aga agt cca aca cca aca tca act caa   432
Pro Pro Met Gln Gly Tyr Arg Arg Ser Pro Thr Pro Thr Ser Thr Gln
    130                 135                 140

tct cca act tct aca tta aga cgc aac tct cag cag aat caa gct cct   480
Ser Pro Thr Ser Thr Leu Arg Arg Asn Ser Gln Gln Asn Gln Ala Pro
145                 150                 155                 160

cca caa tat tct cag caa caa cca caa caa gct caa caa cgt cag aca   528
Pro Gln Tyr Ser Gln Gln Gln Pro Gln Gln Ala Gln Gln Arg Gln Thr
                165                 170                 175

act cct ccg tca aca aaa gct tca tct cga cca cca tct cgt act cgt   576
Thr Pro Pro Ser Thr Lys Ala Ser Ser Arg Pro Pro Ser Arg Thr Arg
            180                 185                 190

gaa cca aag gaa cct gag gta ccc gag aga cca gca gtt att cca ttg   624
Glu Pro Lys Glu Pro Glu Val Pro Glu Arg Pro Ala Val Ile Pro Leu
        195                 200                 205

cca tat gag aag aag gag aaa cca ctg gag aag aaa ggt agt cgt gat   672
Pro Tyr Glu Lys Lys Glu Lys Pro Leu Glu Lys Lys Gly Ser Arg Asp
    210                 215                 220

tct gga aag ggt gat gag aac ctt gaa gag aac att gcc aag atc acg   720
Ser Gly Lys Gly Asp Glu Asn Leu Glu Glu Asn Ile Ala Lys Ile Thr
225                 230                 235                 240

atc gga aag aat aat tgc gag tta tgt ccg gaa caa gaa acg gac ggc   768
Ile Gly Lys Asn Asn Cys Glu Leu Cys Pro Glu Gln Glu Thr Asp Gly
                245                 250                 255

gac cca tct cca cta acc tcc cca atc acc gaa gga aag cca aag aga   816
Asp Pro Ser Pro Leu Thr Ser Pro Ile Thr Glu Gly Lys Pro Lys Arg
            260                 265                 270

gga aag aaa ctt caa cgt aat caa agt gtt gtt gat ttc aat gcc aag   864
Gly Lys Lys Leu Gln Arg Asn Gln Ser Val Val Asp Phe Asn Ala Lys
        275                 280                 285
```


BNSDOCID <WO 0014106A1 >

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aca att gtt act ttg gat aaa att gaa tta caa gtt gag cag ttg aga   912
Thr Ile Val Thr Leu Asp Lys Ile Glu Leu Gln Val Glu Gln Leu Arg
    290                 295                 300

aaa aaa gct gct gaa ctc gaa atg gaa aaa gag caa att ctt cgt tct   960
Lys Lys Ala Ala Glu Leu Glu Met Glu Lys Glu Gln Ile Leu Arg Ser
305                 310                 315                 320

cta gga gaa atc agt gtt cat aac tgc atg ttc aaa ctg gaa gaa tgt   1008
Leu Gly Glu Ile Ser Val His Asn Cys Met Phe Lys Leu Glu Glu Cys
                325                 330                 335

gat cgt gaa gag att gaa gca atc act gac cga ttg aca aaa aga aca   1056
Asp Arg Glu Glu Ile Glu Ala Ile Thr Asp Arg Leu Thr Lys Arg Thr
            340                 345                 350

aag aca gtt caa gtt gtt gtc gaa act cca cga aat gaa gaa cag aaa   1104
Lys Thr Val Gln Val Val Val Glu Thr Pro Arg Asn Glu Glu Gln Lys
        355                 360                 365

aaa gca ctg gaa gat gca act ttg atg atc gat gaa gtc gga gaa atg   1152
Lys Ala Leu Glu Asp Ala Thr Leu Met Ile Asp Glu Val Gly Glu Met
    370                 375                 380

atg cat tcg aat att gaa aag gct aag ctg tgc cta caa acc tac atg   1200
Met His Ser Asn Ile Glu Lys Ala Lys Leu Cys Leu Gln Thr Tyr Met
385                 390                 395                 400

aac gcc tgt tcg tac gaa gaa act gct gga gcc acc tgc caa aac ttc   1248
Asn Ala Cys Ser Tyr Glu Glu Thr Ala Gly Ala Thr Cys Gln Asn Phe
                405                 410                 415

ttg aag atc ata att cag tgc gct gct gat gat cag aaa cgc atc aag   1296
Leu Lys Ile Ile Ile Gln Cys Ala Ala Asp Asp Gln Lys Arg Ile Lys
            420                 425                 430

cgt cgt ctg gaa aat ctg atg tct caa att gag aat gct gag aga acg   1344
Arg Arg Leu Glu Asn Leu Met Ser Gln Ile Glu Asn Ala Glu Arg Thr
        435                 440                 445

aaa gca gat ttg atg gat gat caa agc gaa tag                      1377
Lys Ala Asp Leu Met Asp Asp Gln Ser Glu
    450                 455
```

<210> 14
<211> 458
<212> PRT

BNSDOCID <WO 0014106A1 I >

<213> Caenorhabditis elegans

<400> 14

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Met Pro Val Val Asn Ile Pro Ile Lys Ile Leu Gly Gln Asn Gln Ser
 1               5                  10                  15

His Ser Arg Ser Asn Ser Ser Ser Ser Val Asp Asn Asp Arg Asn Gln
            20                  25                  30

Pro Pro Gln Gln Pro Pro Gln Pro Gln Pro Gln Gln Gln Ser Gln Gln
        35                  40                  45

Gln Tyr Gln Gln Ala Pro Asn Val Asn Thr Asn Met His His Ser Asn
    50                  55                  60

Gly Phe Ser Pro Asn Phe Pro Ser Arg Ser Pro Ile Pro Asp Phe Pro
65                  70                  75                  80

Ser Phe Ser Ser Gly Phe Pro Asn Asp Ser Glu Trp Ser Ser Asn Phe
                85                  90                  95

Pro Ser Phe Pro Asn Phe Pro Ser Gly Phe Ser Asn Gly Ser Ser Asn
            100                 105                 110

Phe Pro Asp Phe Pro Arg Phe Gly Arg Asp Gly Gly Leu Ser Pro Asn
        115                 120                 125

Pro Pro Met Gln Gly Tyr Arg Arg Ser Pro Thr Pro Thr Ser Thr Gln
    130                 135                 140

Ser Pro Thr Ser Thr Leu Arg Arg Asn Ser Gln Gln Asn Gln Ala Pro
145                 150                 155                 160

Pro Gln Tyr Ser Gln Gln Gln Pro Gln Gln Ala Gln Gln Arg Gln Thr
                165                 170                 175

Thr Pro Pro Ser Thr Lys Ala Ser Ser Arg Pro Pro Ser Arg Thr Arg
            180                 185                 190

Glu Pro Lys Glu Pro Glu Val Pro Glu Arg Pro Ala Val Ile Pro Leu
        195                 200                 205

Pro Tyr Glu Lys Lys Glu Lys Pro Leu Glu Lys Lys Gly Ser Arg Asp
    210                 215                 220

Ser Gly Lys Gly Asp Glu Asn Leu Glu Glu Asn Ile Ala Lys Ile Thr
225                 230                 235                 240
```


BNSDOCID <WO 0014106A1 >

```
Ile Gly Lys Asn Asn Cys Glu Leu Cys Pro Glu Gln Glu Thr Asp Gly
                245                 250                 255

Asp Pro Ser Pro Leu Thr Ser Pro Ile Thr Glu Gly Lys Pro Lys Arg
            260                 265                 270

Gly Lys Lys Leu Gln Arg Asn Gln Ser Val Val Asp Phe Asn Ala Lys
        275                 280                 285

Thr Ile Val Thr Leu Asp Lys Ile Glu Leu Gln Val Glu Gln Leu Arg
    290                 295                 300

Lys Lys Ala Ala Glu Leu Glu Met Glu Lys Glu Gln Ile Leu Arg Ser
305                 310                 315                 320

Leu Gly Glu Ile Ser Val His Asn Cys Met Phe Lys Leu Glu Glu Cys
                325                 330                 335

Asp Arg Glu Glu Ile Glu Ala Ile Thr Asp Arg Leu Thr Lys Arg Thr
            340                 345                 350

Lys Thr Val Gln Val Val Val Glu Thr Pro Arg Asn Glu Glu Gln Lys
        355                 360                 365

Lys Ala Leu Glu Asp Ala Thr Leu Met Ile Asp Glu Val Gly Glu Met
    370                 375                 380

Met His Ser Asn Ile Glu Lys Ala Lys Leu Cys Leu Gln Thr Tyr Met
385                 390                 395                 400

Asn Ala Cys Ser Tyr Glu Glu Thr Ala Gly Ala Thr Cys Gln Asn Phe
                405                 410                 415

Leu Lys Ile Ile Ile Gln Cys Ala Ala Asp Asp Gln Lys Arg Ile Lys
            420                 425                 430

Arg Arg Leu Glu Asn Leu Met Ser Gln Ile Glu Asn Ala Glu Arg Thr
        435                 440                 445

Lys Ala Asp Leu Met Asp Asp Gln Ser Glu
    450                 455
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<210> 15
<211> 588
<212> DNA
<213> Schizosaccharomyces pombe

BNSDOCID <WO 0014106A1 I >

<220>
<221> CDS
<222> (1)..(588)

<400> 15

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atg tca gaa aag act agc aca gtt aca ata cac tat gga aat cag cga   48
Met Ser Glu Lys Thr Ser Thr Val Thr Ile His Tyr Gly Asn Gln Arg
  1               5                  10                  15

ttt ccg gta gca gtc aat cta aat gag acg tta agt gaa ctg att gat   96
Phe Pro Val Ala Val Asn Leu Asn Glu Thr Leu Ser Glu Leu Ile Asp
             20                  25                  30

gat tta ctt gaa acg act gag att tct gag aag aaa gtc aag ctt ttt  144
Asp Leu Leu Glu Thr Thr Glu Ile Ser Glu Lys Lys Val Lys Leu Phe
         35                  40                  45

tac gct ggc aag cgt tta aaa gac aaa aaa gcc tcg tta tca aaa ttg  192
Tyr Ala Gly Lys Arg Leu Lys Asp Lys Lys Ala Ser Leu Ser Lys Leu
     50                  55                  60

ggt tta aaa aat cat agt aaa att cta tgt ata aga cca cat aag caa  240
Gly Leu Lys Asn His Ser Lys Ile Leu Cys Ile Arg Pro His Lys Gln
 65                  70                  75                  80

caa cga ggt tcc aag gaa aaa gac acg gtt gag ccc gct ccg aaa gcg  288
Gln Arg Gly Ser Lys Glu Lys Asp Thr Val Glu Pro Ala Pro Lys Ala
                 85                  90                  95

gaa gcg gag aat cct gta ttt tcg cgt att tct gga gaa ata aaa gcc  336
Glu Ala Glu Asn Pro Val Phe Ser Arg Ile Ser Gly Glu Ile Lys Ala
            100                 105                 110

atc gat cag tat gtt gac aaa gaa ctt tcc ccc atg tac gac aat tac  384
Ile Asp Gln Tyr Val Asp Lys Glu Leu Ser Pro Met Tyr Asp Asn Tyr
        115                 120                 125

gta aat aaa ccg tcg aac gat cca aag cag aaa aac aaa cag aaa cta  432
Val Asn Lys Pro Ser Asn Asp Pro Lys Gln Lys Asn Lys Gln Lys Leu
    130                 135                 140

atg ata agt gaa cta ctt tta caa cag ctt tta aaa ttg gat gga gtt  480
Met Ile Ser Glu Leu Leu Leu Gln Gln Leu Leu Lys Leu Asp Gly Val
145                 150                 155                 160

gac gta ctg ggc agc gag aaa ttg cgt ttt gaa cgg aag caa ctt gtt  528
Asp Val Leu Gly Ser Glu Lys Leu Arg Phe Glu Arg Lys Gln Leu Val
                165                 170                 175
```


BNSDOCID <WO 0014106A1 >

```
tct aag atc caa aaa atg ttg gat cac gtt gac caa aca agc caa gaa   576
Ser Lys Ile Gln Lys Met Leu Asp His Val Asp Gln Thr Ser Gln Glu
            180                 185                 190

gtg gcc gca tag                                                  588
Val Ala Ala
        195
```

<210> 16
<211> 195
<212> PRT
<213> Schizosaccharomyces pombe

<400> 16

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Met Ser Glu Lys Thr Ser Thr Val Thr Ile His Tyr Gly Asn Gln Arg
  1               5                  10                  15

Phe Pro Val Ala Val Asn Leu Asn Glu Thr Leu Ser Glu Leu Ile Asp
             20                  25                  30

Asp Leu Leu Glu Thr Thr Glu Ile Ser Glu Lys Lys Val Lys Leu Phe
         35                  40                  45

Tyr Ala Gly Lys Arg Leu Lys Asp Lys Lys Ala Ser Leu Ser Lys Leu
     50                  55                  60

Gly Leu Lys Asn His Ser Lys Ile Leu Cys Ile Arg Pro His Lys Gln
 65                  70                  75                  80

Gln Arg Gly Ser Lys Glu Lys Asp Thr Val Glu Pro Ala Pro Lys Ala
                 85                  90                  95

Glu Ala Glu Asn Pro Val Phe Ser Arg Ile Ser Gly Glu Ile Lys Ala
            100                 105                 110

Ile Asp Gln Tyr Val Asp Lys Glu Leu Ser Pro Met Tyr Asp Asn Tyr
        115                 120                 125

Val Asn Lys Pro Ser Asn Asp Pro Lys Gln Lys Asn Lys Gln Lys Leu
    130                 135                 140

Met Ile Ser Glu Leu Leu Leu Gln Gln Leu Leu Lys Leu Asp Gly Val
145                 150                 155                 160

Asp Val Leu Gly Ser Glu Lys Leu Arg Phe Glu Arg Lys Gln Leu Val
                165                 170                 175
```


BNSDOCID <WO 0014106A1 I >

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Ser Lys Ile Gln Lys Met Leu Asp His Val Asp Gln Thr Ser Gln Glu
            180                 185                 190

Val Ala Ala
        195


<210> 17
<211> 621
<212> DNA
<213> Schizosaccharomyces pombe

<220>
<221> CDS
<222> (1)..(621)

<400> 17
atg tct ttt ttt acc cag ttg tgt tct atg gat aaa aaa tat tgg atc   48
Met Ser Phe Phe Thr Gln Leu Cys Ser Met Asp Lys Lys Tyr Trp Ile
  1               5                  10                  15

tct cta gct gta ttg tca gtt act gtt ttg att agc gca tta ttg aaa   96
Ser Leu Ala Val Leu Ser Val Thr Val Leu Ile Ser Ala Leu Leu Lys
             20                  25                  30

aag aga gct act gaa acc gaa gat att gtc gtt gtt cat tac gat ggc   144
Lys Arg Ala Thr Glu Thr Glu Asp Ile Val Val Val His Tyr Asp Gly
         35                  40                  45

gaa aag ttg aat ttt gtg ttg cga caa cca agg ctg aat atg gtt tct   192
Glu Lys Leu Asn Phe Val Leu Arg Gln Pro Arg Leu Asn Met Val Ser
     50                  55                  60

tac act agt ttt ctt cgt cgc gtg tgc aac gca ttt tca gta atg ccc   240
Tyr Thr Ser Phe Leu Arg Arg Val Cys Asn Ala Phe Ser Val Met Pro
 65                  70                  75                  80

gac aaa gcg tct ctc aag tta aac ggg gtg acc ctc aag gat ggt tca   288
Asp Lys Ala Ser Leu Lys Leu Asn Gly Val Thr Leu Lys Asp Gly Ser
                 85                  90                  95

ctt tcc gac caa aat gtg caa aat gga agt gaa tta gag ctc gaa tta   336
Leu Ser Asp Gln Asn Val Gln Asn Gly Ser Glu Leu Glu Leu Glu Leu
            100                 105                 110

ccc aaa ctg agc ccg gca atg caa caa att gaa gca tat ata gat gag   384
Pro Lys Leu Ser Pro Ala Met Gln Gln Ile Glu Ala Tyr Ile Asp Glu
```


BNSDOCID <WO__0014106A1_I_>

```
        115                 120                 125

ctt caa cag gat ctc gtc cct aaa att gaa gcc ttc tgc caa tcg tct   432
Leu Gln Gln Asp Leu Val Pro Lys Ile Glu Ala Phe Cys Gln Ser Ser
    130                 135                 140

ccc gct tcg gca caa gat gtt caa gat ttg cat aca cgc ctt agt gaa   480
Pro Ala Ser Ala Gln Asp Val Gln Asp Leu His Thr Arg Leu Ser Glu
145                 150                 155                 160

aca ttg ttg gct agg atg ata aaa tta gat gct gtt aat gtt gaa gac   528
Thr Leu Leu Ala Arg Met Ile Lys Leu Asp Ala Val Asn Val Glu Asp
                165                 170                 175

gac cca gaa gct cgt ctt aaa aga aaa gaa gct att cgt tta tct caa   576
Asp Pro Glu Ala Arg Leu Lys Arg Lys Glu Ala Ile Arg Leu Ser Gln
            180                 185                 190

caa tat ttg agt aaa cta gat tcc acc aag aat caa aac aaa tga       621
Gln Tyr Leu Ser Lys Leu Asp Ser Thr Lys Asn Gln Asn Lys
        195                 200                 205
```

<210> 18
<211> 206
<212> PRT
<213> Schizosaccharomyces pombe

<400> 18

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Met Ser Phe Phe Thr Gln Leu Cys Ser Met Asp Lys Lys Tyr Trp Ile
  1               5                  10                  15

Ser Leu Ala Val Leu Ser Val Thr Val Leu Ile Ser Ala Leu Leu Lys
             20                  25                  30

Lys Arg Ala Thr Glu Thr Glu Asp Ile Val Val Val His Tyr Asp Gly
         35                  40                  45

Glu Lys Leu Asn Phe Val Leu Arg Gln Pro Arg Leu Asn Met Val Ser
     50                  55                  60

Tyr Thr Ser Phe Leu Arg Arg Val Cys Asn Ala Phe Ser Val Met Pro
 65                  70                  75                  80

Asp Lys Ala Ser Leu Lys Leu Asn Gly Val Thr Leu Lys Asp Gly Ser
                 85                  90                  95

Leu Ser Asp Gln Asn Val Gln Asn Gly Ser Glu Leu Glu Leu Glu Leu
```


BNSDOCID <WO 0014106A1 I >

100 105 110

Pro Lys Leu Ser Pro Ala Met Gln Gln Ile Glu Ala Tyr Ile Asp Glu
115 120 125

Leu Gln Gln Asp Leu Val Pro Lys Ile Glu Ala Phe Cys Gln Ser Ser
130 135 140

Pro Ala Ser Ala Gln Asp Val Gln Asp Leu His Thr Arg Leu Ser Glu
145 150 155 160

Thr Leu Leu Ala Arg Met Ile Lys Leu Asp Ala Val Asn Val Glu Asp
165 170 175

Asp Pro Glu Ala Arg Leu Lys Arg Lys Glu Ala Ile Arg Leu Ser Gln
180 185 190

Gln Tyr Leu Ser Lys Leu Asp Ser Thr Lys Asn Gln Asn Lys
195 200 205

<210> 19
<211> 2534
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (307)..(2034)

<400> 19
gcggagctcc gcatccaacc ccgggccgcg gccaacttct ctggactgga ccagaagttt 60

ctagccggcc agttgctacc tccctttatc tcctccttcc cctctggcag cgaggaggct 120

atttccagac acttccaccc ctctctggcc acgtcacccc cgcctttaat tcataaaggt 180

gcccggcgcc ggcttcccgg acacgtcggc ggcggagagg ggcccacggc ggcggcccgg 240

ccagagactc ggcgcccgga gccagcgccc cgcacccgcg ccccagcggg cagaccccaa 300

cccagc atg agc gcc gcc acc cac tcg ccc atg atg cag gtg gcg tcc 348
Met Ser Ala Ala Thr His Ser Pro Met Met Gln Val Ala Ser
1 5 10

ggc aac ggt gac cgc gac cct ttg ccc ccc gga tgg gag atc aag atc 396
Gly Asn Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp Glu Ile Lys Ile
15 20 25 30

BNSDOCID <WO 0014106A1_I >

```
gac ccg cag acc ggc tgg ccc ttc ttc gtg gac cac aac agc cgc acc   444
Asp Pro Gln Thr Gly Trp Pro Phe Phe Val Asp His Asn Ser Arg Thr
                35                  40                  45

act acg tgg aac gac ccg cgc gtg ccc tct gag ggc ccc aag gag act   492
Thr Thr Trp Asn Asp Pro Arg Val Pro Ser Glu Gly Pro Lys Glu Thr
            50                  55                  60

cca tcc tct gcc aat ggc cct tcc cgg gag ggc tct agg ctg ccg cct   540
Pro Ser Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser Arg Leu Pro Pro
        65                  70                  75

gct agg gaa ggc cac cct gtg tac ccc cag ctc cga cca ggc tac att   588
Ala Arg Glu Gly His Pro Val Tyr Pro Gln Leu Arg Pro Gly Tyr Ile
    80                  85                  90

ccc att cct gtg ctc cat gaa ggc gct gag aac cgg cag gtg cac cct   636
Pro Ile Pro Val Leu His Glu Gly Ala Glu Asn Arg Gln Val His Pro
95                  100                 105                 110

ttc cat gtc tat ccc cag cct ggg atg cag cga ttc cga act gag gcg   684
Phe His Val Tyr Pro Gln Pro Gly Met Gln Arg Phe Arg Thr Glu Ala
                115                 120                 125

gca gca gcg gct cct cag agg tcc cag tca cct ctg cgg ggc atg cca   732
Ala Ala Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu Arg Gly Met Pro
            130                 135                 140

gaa acc act cag cca gat aaa cag tgt gga cag gtg gca gcg gcg gcg   780
Glu Thr Thr Gln Pro Asp Lys Gln Cys Gly Gln Val Ala Ala Ala Ala
        145                 150                 155

gca gcc cag ccc cca gcc tcc cac gga cct gag cgg tcc cag tct cca   828
Ala Ala Gln Pro Pro Ala Ser His Gly Pro Glu Arg Ser Gln Ser Pro
    160                 165                 170

gct gcc tct gac tgc tca tcc tca tcc tcc tcg gcc agc ctg cct tcc   876
Ala Ala Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala Ser Leu Pro Ser
175                 180                 185                 190

tcc ggc agg agc agc ctg ggc agt cac cag ctc ccg cgg ggg tac atc   924
Ser Gly Arg Ser Ser Leu Gly Ser His Gln Leu Pro Arg Gly Tyr Ile
                195                 200                 205

tcc att ccg gtg ata cac gag cag aac gtt acc cgg cca gca gcc cag   972
Ser Ile Pro Val Ile His Glu Gln Asn Val Thr Arg Pro Ala Ala Gln
            210                 215                 220
```


BNSDOCID <WO 0014106A1 | >

```
ccc tcc ttc cac aaa gcc cag aag acg cac tac cca gcg cag agg ggt   1020
Pro Ser Phe His Lys Ala Gln Lys Thr His Tyr Pro Ala Gln Arg Gly
        225                 230                 235

gag tac cag acc cac cag cct gtg tac cac aag atc cag ggg gat gac   1068
Glu Tyr Gln Thr His Gln Pro Val Tyr His Lys Ile Gln Gly Asp Asp
    240                 245                 250

tgg gag ccc cgg ccc ctg cgg gcg gca tcc ccg ttc agg tca tct gtc   1116
Trp Glu Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe Arg Ser Ser Val
255                 260                 265                 270

cag ggt gca tcg agc cgg gag ggc tca cca gcc agg agc agc acg cca   1164
Gln Gly Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg Ser Ser Thr Pro
                275                 280                 285

ctc cac tcc ccc tcg ccc atc cgt gtg cac acc gtg gtc gac agg cct   1212
Leu His Ser Pro Ser Pro Ile Arg Val His Thr Val Val Asp Arg Pro
            290                 295                 300

cag cag ccc atg acc cat cga gaa act gca cct gtt tcc cag cct gaa   1260
Gln Gln Pro Met Thr His Arg Glu Thr Ala Pro Val Ser Gln Pro Glu
        305                 310                 315

aac aaa cca gaa agt aag cca ggc cca gtt gga cca gaa ctc cct cct   1308
Asn Lys Pro Glu Ser Lys Pro Gly Pro Val Gly Pro Glu Leu Pro Pro
    320                 325                 330

gga cac atc cca att caa gtg atc cgc aaa gag gtg gat tct aaa cct   1356
Gly His Ile Pro Ile Gln Val Ile Arg Lys Glu Val Asp Ser Lys Pro
335                 340                 345                 350

gtt tcc cag aag ccc cca cct ccc tct gag aag gta gag gtg aaa gtt   1404
Val Ser Gln Lys Pro Pro Pro Pro Ser Glu Lys Val Glu Val Lys Val
                355                 360                 365

ccc cct gct cca gtt cct tgt cct cct ccc agc cct ggc cct tct gct   1452
Pro Pro Ala Pro Val Pro Cys Pro Pro Pro Ser Pro Gly Pro Ser Ala
            370                 375                 380

gtc ccc tct tcc ccc aag agt gtg gct aca gaa gag agg gca gcc ccc   1500
Val Pro Ser Ser Pro Lys Ser Val Ala Thr Glu Glu Arg Ala Ala Pro
        385                 390                 395

agc act gcc cct gca gaa gct aca cct cca aaa cca gga gaa gcc gag   1548
Ser Thr Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro Gly Glu Ala Glu
    400                 405                 410
```


BNSDOCID <WO _ 0014106A1 | >

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gct ccc cca aaa cat cca gga gtg ctg aaa gtg gaa gcc atc ctg gag   1596
Ala Pro Pro Lys His Pro Gly Val Leu Lys Val Glu Ala Ile Leu Glu
415                 420                 425                 430

aag gtg cag ggg ctg gag cag gct gta gac aac ttt gaa ggc aag aag   1644
Lys Val Gln Gly Leu Glu Gln Ala Val Asp Asn Phe Glu Gly Lys Lys
                435                 440                 445

act gac aaa aag tac ctg atg atc gaa gag tat ttg acc aaa gag ctg   1692
Thr Asp Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu Thr Lys Glu Leu
            450                 455                 460

ctg gcc ctg gat tca gtg gac ccc gag gga cga gcc gat gtg cgt cag   1740
Leu Ala Leu Asp Ser Val Asp Pro Glu Gly Arg Ala Asp Val Arg Gln
        465                 470                 475

gcc agg aga gac ggt gtc agg aag gtt cag acc atc ttg gaa aaa ctt   1788
Ala Arg Arg Asp Gly Val Arg Lys Val Gln Thr Ile Leu Glu Lys Leu
    480                 485                 490

gaa cag aaa gcc att gat gtc cca ggt caa gtc cag gtc tat gaa ctc   1836
Glu Gln Lys Ala Ile Asp Val Pro Gly Gln Val Gln Val Tyr Glu Leu
495                 500                 505                 510

cag ccc agc aac ctt gaa gca gat cag cca ctg cag gca atc atg gag   1884
Gln Pro Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln Ala Ile Met Glu
                515                 520                 525

atg ggt gcc gtg gca gca gac aag ggc aag aaa aat gct gga aat gca   1932
Met Gly Ala Val Ala Ala Asp Lys Gly Lys Lys Asn Ala Gly Asn Ala
            530                 535                 540

gaa gat ccc cac aca gaa acc cag cag cca gaa gcc aca gca gca gcg   1980
Glu Asp Pro His Thr Glu Thr Gln Gln Pro Glu Ala Thr Ala Ala Ala
        545                 550                 555

act tca aac ccc agc agc atg aca gac acc cct ggt aac cca gca gca   2028
Thr Ser Asn Pro Ser Ser Met Thr Asp Thr Pro Gly Asn Pro Ala Ala
    560                 565                 570

ccg tag cctctgccct gtaaaaatca gactcggaac cgatgtgtgc tttagggaat   2084
Pro
575

tttaagttgc atgcatttca gagactttaa gtcagttggt ttttattagc tgcttggtat 2144

gcagtaactt gggtggaggc aaaacactaa taaaagggct aaaaaggaaa atgatgcttt 2204
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tcttctatat tcttactctg tacaaataaa gaagttgctt gttgtttgag aagtttaacc 2264

ccgttgcttg ttctgcagcc ctgtctactt gggcaccccc accacctgtt agctgtggtt 2324

gtgcactgtc ttttgtagct ctggactgga ggggtagatg gggagtcaat tacccatcac 2384

ataaatatga aacatttatc agaaatgttg ccattttaat gagatgattt tcttcatctc 2444

ataattaaaa tacctgactt tagagagagt aaaatgtgcc aggagccata ggaatatctg 2504

tatgttggat gactttaatg ctacattttc 2534

<210> 20
<211> 575
<212> PRT
<213> Homo sapiens

<400> 20

Met Ser Ala Ala Thr His Ser Pro Met Met Gln Val Ala Ser Gly Asn
1 5 10 15

Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp Glu Ile Lys Ile Asp Pro
20 25 30

Gln Thr Gly Trp Pro Phe Phe Val Asp His Asn Ser Arg Thr Thr Thr
35 40 45

Trp Asn Asp Pro Arg Val Pro Ser Glu Gly Pro Lys Glu Thr Pro Ser
50 55 60

Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser Arg Leu Pro Pro Ala Arg
65 70 75 80

Glu Gly His Pro Val Tyr Pro Gln Leu Arg Pro Gly Tyr Ile Pro Ile
85 90 95

Pro Val Leu His Glu Gly Ala Glu Asn Arg Gln Val His Pro Phe His
100 105 110

Val Tyr Pro Gln Pro Gly Met Gln Arg Phe Arg Thr Glu Ala Ala Ala
115 120 125

Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu Arg Gly Met Pro Glu Thr
130 135 140

Thr Gln Pro Asp Lys Gln Cys Gly Gln Val Ala Ala Ala Ala Ala Ala

BNSDOCID <WO___0014106A1 >

145 150 155 160

Gln Pro Pro Ala Ser His Gly Pro Glu Arg Ser Gln Ser Pro Ala Ala
165 170 175

Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala Ser Leu Pro Ser Ser Gly
180 185 190

Arg Ser Ser Leu Gly Ser His Gln Leu Pro Arg Gly Tyr Ile Ser Ile
195 200 205

Pro Val Ile His Glu Gln Asn Val Thr Arg Pro Ala Ala Gln Pro Ser
210 215 220

Phe His Lys Ala Gln Lys Thr His Tyr Pro Ala Gln Arg Gly Glu Tyr
225 230 235 240

Gln Thr His Gln Pro Val Tyr His Lys Ile Gln Gly Asp Asp Trp Glu
245 250 255

Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe Arg Ser Ser Val Gln Gly
260 265 270

Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg Ser Ser Thr Pro Leu His
275 280 285

Ser Pro Ser Pro Ile Arg Val His Thr Val Val Asp Arg Pro Gln Gln
290 295 300

Pro Met Thr His Arg Glu Thr Ala Pro Val Ser Gln Pro Glu Asn Lys
305 310 315 320

Pro Glu Ser Lys Pro Gly Pro Val Gly Pro Glu Leu Pro Pro Gly His
325 330 335

Ile Pro Ile Gln Val Ile Arg Lys Glu Val Asp Ser Lys Pro Val Ser
340 345 350

Gln Lys Pro Pro Pro Pro Ser Glu Lys Val Glu Val Lys Val Pro Pro
355 360 365

Ala Pro Val Pro Cys Pro Pro Pro Ser Pro Gly Pro Ser Ala Val Pro
370 375 380

Ser Ser Pro Lys Ser Val Ala Thr Glu Glu Arg Ala Ala Pro Ser Thr
385 390 395 400

Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro Gly Glu Ala Glu Ala Pro

BNSDOCID <WO 0014106A1 | >

405 410 415

Pro Lys His Pro Gly Val Leu Lys Val Glu Ala Ile Leu Glu Lys Val
420 425 430

Gln Gly Leu Glu Gln Ala Val Asp Asn Phe Glu Gly Lys Lys Thr Asp
435 440 445

Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu Thr Lys Glu Leu Leu Ala
450 455 460

Leu Asp Ser Val Asp Pro Glu Gly Arg Ala Asp Val Arg Gln Ala Arg
465 470 475 480

Arg Asp Gly Val Arg Lys Val Gln Thr Ile Leu Glu Lys Leu Glu Gln
485 490 495

Lys Ala Ile Asp Val Pro Gly Gln Val Gln Val Tyr Glu Leu Gln Pro
500 505 510

Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln Ala Ile Met Glu Met Gly
515 520 525

Ala Val Ala Ala Asp Lys Gly Lys Lys Asn Ala Gly Asn Ala Glu Asp
530 535 540

Pro His Thr Glu Thr Gln Gln Pro Glu Ala Thr Ala Ala Ala Thr Ser
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Asn Pro Ser Ser Met Thr Asp Thr Pro Gly Asn Pro Ala Ala Pro
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<213> Homo sapiens

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<222> (43)..(1416)

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Met Ser Ala Leu
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BNSDOCID <WO 0014106A1_I_>

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Arg Arg Ser Gly Tyr Gly Pro Ser Asp Gly Pro Ser Tyr Gly Arg Tyr
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tac ggg cct ggg ggt gga gat gtg ccg gta cac cca cct cca ccc tta   150
Tyr Gly Pro Gly Gly Gly Asp Val Pro Val His Pro Pro Pro Pro Leu
                25                  30                  35

tat cct ctt cgc cct gaa cct ccc cag cct ccc att tcc tgg cgg gtg   198
Tyr Pro Leu Arg Pro Glu Pro Pro Gln Pro Pro Ile Ser Trp Arg Val
            40                  45                  50

cgc ggg ggc ggc ccg gcg gag acc acc tgg ctg gga gaa ggc gga gga   246
Arg Gly Gly Gly Pro Ala Glu Thr Thr Trp Leu Gly Glu Gly Gly Gly
        55                  60                  65

ggc gat ggc tac tat ccc tcg gga ggc gcc tgg cca gag cct ggt cga   294
Gly Asp Gly Tyr Tyr Pro Ser Gly Gly Ala Trp Pro Glu Pro Gly Arg
    70                  75                  80

gcc gga gga agc cac cag gag cag cca cca tat cct agc tac aat tct   342
Ala Gly Gly Ser His Gln Glu Gln Pro Pro Tyr Pro Ser Tyr Asn Ser
85                  90                  95                  100

aac tat tgg aat tct act gcg aga tct agg gct cct tac cca agt aca   390
Asn Tyr Trp Asn Ser Thr Ala Arg Ser Arg Ala Pro Tyr Pro Ser Thr
                105                 110                 115

tat cct gta aga cca gaa ttg caa ggc cag agt ttg aat tct tat aca   438
Tyr Pro Val Arg Pro Glu Leu Gln Gly Gln Ser Leu Asn Ser Tyr Thr
            120                 125                 130

aat gga gcg tat ggt cca aca tac ccc cca ggc cct ggg gca aat act   486
Asn Gly Ala Tyr Gly Pro Thr Tyr Pro Pro Gly Pro Gly Ala Asn Thr
        135                 140                 145

gcc tca tac tca ggg gct tat tat gca cct ggt tat act cag acc agt   534
Ala Ser Tyr Ser Gly Ala Tyr Tyr Ala Pro Gly Tyr Thr Gln Thr Ser
    150                 155                 160

tac tcc aca gaa gtt cca agt act tac cgt tca tct ggc aac agc cca   582
Tyr Ser Thr Glu Val Pro Ser Thr Tyr Arg Ser Ser Gly Asn Ser Pro
165                 170                 175                 180

act cca gtc tct cgt tgg atc tat ccc cag cag gac tgt cag act gaa   630
Thr Pro Val Ser Arg Trp Ile Tyr Pro Gln Gln Asp Cys Gln Thr Glu
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gca ccc cct ctt agg ggg cag gtt cca gga tat ccg cct tca cag aac   678
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BNSDOCID <WO 0014106A1 | >

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Ala Pro Pro Leu Arg Gly Gln Val Pro Gly Tyr Pro Pro Ser Gln Asn
            200                 205                 210

cct gga atg acc ctg ccc cat tat cct tat gga gat ggt aat cgt agt   726
Pro Gly Met Thr Leu Pro His Tyr Pro Tyr Gly Asp Gly Asn Arg Ser
        215                 220                 225

gtt cca caa tca gga ccg act gta cga cca caa gaa gat gcg tgg gct   774
Val Pro Gln Ser Gly Pro Thr Val Arg Pro Gln Glu Asp Ala Trp Ala
    230                 235                 240

tct cct ggt gct tat gga atg ggt ggc cgt tat ccc tgg cct tca tca   822
Ser Pro Gly Ala Tyr Gly Met Gly Gly Arg Tyr Pro Trp Pro Ser Ser
245                 250                 255                 260

gcg ccc tca gca cca ccc ggc aat ctc tac atg act gaa agt act tca   870
Ala Pro Ser Ala Pro Pro Gly Asn Leu Tyr Met Thr Glu Ser Thr Ser
                265                 270                 275

cca tgg cct agc agt ggc tct ccc cag tca ccc cct tca ccc cca gtc   918
Pro Trp Pro Ser Ser Gly Ser Pro Gln Ser Pro Pro Ser Pro Pro Val
            280                 285                 290

cag cag ccc aag gat tct tca tac ccc tat agc caa tca gat caa agc   966
Gln Gln Pro Lys Asp Ser Ser Tyr Pro Tyr Ser Gln Ser Asp Gln Ser
        295                 300                 305

atg aac cgg cac aac ttt cct tgc agt gtc cat cag tac gaa tcc tcg   1014
Met Asn Arg His Asn Phe Pro Cys Ser Val His Gln Tyr Glu Ser Ser
    310                 315                 320

ggg aca gtg atc aat gaa gat tca gat ctt ttg gat tcc caa gtc cag   1062
Gly Thr Val Ile Asn Glu Asp Ser Asp Leu Leu Asp Ser Gln Val Gln
325                 330                 335                 340

tat agt gct gag cct cag ctg tat ggt aat gcc acc agt gac cat ccc   1110
Tyr Ser Ala Glu Pro Gln Leu Tyr Gly Asn Ala Thr Ser Asp His Pro
                345                 350                 355

aac aat caa gat caa agt agc agt ctt cct gaa gaa tgt gta cct tca   1158
Asn Asn Gln Asp Gln Ser Ser Ser Leu Pro Glu Glu Cys Val Pro Ser
            360                 365                 370

gat gaa agt act cct ccg agt att aaa aaa atc ata cat gtg ctg gag   1206
Asp Glu Ser Thr Pro Pro Ser Ile Lys Lys Ile Ile His Val Leu Glu
        375                 380                 385

aag gtc cag tat ctt gaa caa gaa gta gaa gaa ttt gta gga aaa aag   1254
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BNSDOCID <WO 0014106A1_ >

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Lys Val Gln Tyr Leu Glu Gln Glu Val Glu Glu Phe Val Gly Lys Lys
    390                 395                 400

aca gac aaa gca tac tgg ctt ctg gaa gaa atg cta acc aag gaa ctt   1302
Thr Asp Lys Ala Tyr Trp Leu Leu Glu Glu Met Leu Thr Lys Glu Leu
405                 410                 415                 420

ttg gaa ctg gat tca gtt gaa act ggg ggc cag gac tct gta cgg cag   1350
Leu Glu Leu Asp Ser Val Glu Thr Gly Gly Gln Asp Ser Val Arg Gln
                425                 430                 435

gcc aga aaa gag gct gtt tgt aag att cag gcc ata ctg gaa aaa tta   1398
Ala Arg Lys Glu Ala Val Cys Lys Ile Gln Ala Ile Leu Glu Lys Leu
            440                 445                 450

gaa aaa aaa gga tta tga aaggatttag aacaaagtgg aagcctgtta          1446
Glu Lys Lys Gly Leu
        455

ctaacttgac caaagaacac ttgattaggt taattaccct ctttttgaaa tgcctgttga 1506

tgacaagaag caatacattc cagcttttcc tttgatttta tacttgaaaa actggcaaag 1566

gaatggaaga atattttagt catgaagttg ttttcagttt tcagacgaat gaatgtaata 1626

ggaaactatg gagttaccaa tattgccaag tagactcact ccttaaaaaa tttatggata 1686

tctacaagct gcttattacc agcaggaggg aaacacactt cacacaacag gcttatcaga 1746

aacctaccag atgaaactgg atataatttg agacaaacag gatgtgtttt tttaaacatc 1806

tggatatctt gtcacatttt tgtacattgt gactgctttc aacatatact tcatgtgtaa 1866

ttatagctta gactttagcc ttcttggact tctgttttgt tttgttattt gcagtttaca 1926

aatatagtat tattctctaa aaaaaaaaaa aaaaaaaaaa                       1966


<210> 22
<211> 457
<212> PRT
<213> Homo sapiens

<400> 22
Met Ser Ala Leu Arg Arg Ser Gly Tyr Gly Pro Ser Asp Gly Pro Ser
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Tyr Gly Arg Tyr Tyr Gly Pro Gly Gly Gly Asp Val Pro Val His Pro
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Pro Pro Pro Leu Tyr Pro Leu Arg Pro Glu Pro Pro Gln Pro Pro Ile
35 40 45

Ser Trp Arg Val Arg Gly Gly Gly Pro Ala Glu Thr Thr Trp Leu Gly
50 55 60

Glu Gly Gly Gly Gly Asp Gly Tyr Tyr Pro Ser Gly Gly Ala Trp Pro
65 70 75 80

Glu Pro Gly Arg Ala Gly Gly Ser His Gln Glu Gln Pro Pro Tyr Pro
85 90 95

Ser Tyr Asn Ser Asn Tyr Trp Asn Ser Thr Ala Arg Ser Arg Ala Pro
100 105 110

Tyr Pro Ser Thr Tyr Pro Val Arg Pro Glu Leu Gln Gly Gln Ser Leu
115 120 125

Asn Ser Tyr Thr Asn Gly Ala Tyr Gly Pro Thr Tyr Pro Pro Gly Pro
130 135 140

Gly Ala Asn Thr Ala Ser Tyr Ser Gly Ala Tyr Tyr Ala Pro Gly Tyr
145 150 155 160

Thr Gln Thr Ser Tyr Ser Thr Glu Val Pro Ser Thr Tyr Arg Ser Ser
165 170 175

Gly Asn Ser Pro Thr Pro Val Ser Arg Trp Ile Tyr Pro Gln Gln Asp
180 185 190

Cys Gln Thr Glu Ala Pro Pro Leu Arg Gly Gln Val Pro Gly Tyr Pro
195 200 205

Pro Ser Gln Asn Pro Gly Met Thr Leu Pro His Tyr Pro Tyr Gly Asp
210 215 220

Gly Asn Arg Ser Val Pro Gln Ser Gly Pro Thr Val Arg Pro Gln Glu
225 230 235 240

Asp Ala Trp Ala Ser Pro Gly Ala Tyr Gly Met Gly Gly Arg Tyr Pro
245 250 255

Trp Pro Ser Ser Ala Pro Ser Ala Pro Pro Gly Asn Leu Tyr Met Thr
260 265 270

Glu Ser Thr Ser Pro Trp Pro Ser Ser Gly Ser Pro Gln Ser Pro Pro

BNSDOCID <WO_ 0014106A' I_>

275 280 285

Ser Pro Pro Val Gln Gln Pro Lys Asp Ser Ser Tyr Pro Tyr Ser Gln
290 295 300

Ser Asp Gln Ser Met Asn Arg His Asn Phe Pro Cys Ser Val His Gln
305 310 315 320

Tyr Glu Ser Ser Gly Thr Val Ile Asn Glu Asp Ser Asp Leu Leu Asp
325 330 335

Ser Gln Val Gln Tyr Ser Ala Glu Pro Gln Leu Tyr Gly Asn Ala Thr
340 345 350

Ser Asp His Pro Asn Asn Gln Asp Gln Ser Ser Ser Leu Pro Glu Glu
355 360 365

Cys Val Pro Ser Asp Glu Ser Thr Pro Pro Ser Ile Lys Lys Ile Ile
370 375 380

His Val Leu Glu Lys Val Gln Tyr Leu Glu Gln Glu Val Glu Glu Phe
385 390 395 400

Val Gly Lys Lys Thr Asp Lys Ala Tyr Trp Leu Leu Glu Glu Met Leu
405 410 415

Thr Lys Glu Leu Leu Glu Leu Asp Ser Val Glu Thr Gly Gly Gln Asp
420 425 430

Ser Val Arg Gln Ala Arg Lys Glu Ala Val Cys Lys Ile Gln Ala Ile
435 440 445

Leu Glu Lys Leu Glu Lys Lys Gly Leu
450 455

<210> 23
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<212> DNA
<213> Homo sapiens

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<222> (247)..(1590)

<400> 23
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gcccagctcc ggtgccgcac cccgtaaagg gctgatcttc cacctcgcca cctcagccac 180

gggacgccaa gaccgcatcc aattcagact tcttttggtg cttgtgaaac tgaacacaac 240

aaaagt atg gat atg gga aac caa cat cct tct att agt agg ctt cag    288
       Met Asp Met Gly Asn Gln His Pro Ser Ile Ser Arg Leu Gln
         1               5                  10

gaa atc caa aag gaa gta aaa agt gta gaa cag caa gtt atc ggc ttc   336
Glu Ile Gln Lys Glu Val Lys Ser Val Glu Gln Gln Val Ile Gly Phe
 15                  20                  25                  30

agt ggt ctg tca gat gac aag aat tac aag aaa ctg gag agg att cta   384
Ser Gly Leu Ser Asp Asp Lys Asn Tyr Lys Lys Leu Glu Arg Ile Leu
                 35                  40                  45

aca aaa cag ctt ttt gaa ata gac tct gta gat act gaa gga aaa gga   432
Thr Lys Gln Leu Phe Glu Ile Asp Ser Val Asp Thr Glu Gly Lys Gly
             50                  55                  60

gat att cag caa gct agg aag cgg gca gca cag gag aca gaa cgt ctt   480
Asp Ile Gln Gln Ala Arg Lys Arg Ala Ala Gln Glu Thr Glu Arg Leu
         65                  70                  75

ctc aaa gag ttg gag cag aat gca aac cac cca cac cgg att gaa ata   528
Leu Lys Glu Leu Glu Gln Asn Ala Asn His Pro His Arg Ile Glu Ile
     80                  85                  90

cag aac att ttt gag gaa gcc cag tcc ctc gtg aga gag aaa att gtg   576
Gln Asn Ile Phe Glu Glu Ala Gln Ser Leu Val Arg Glu Lys Ile Val
 95                  100                 105                 110

cca ttt tat aat gga ggc aac tgc gta act gat gag ttt gaa gaa ggc   624
Pro Phe Tyr Asn Gly Gly Asn Cys Val Thr Asp Glu Phe Glu Glu Gly
                115                 120                 125

atc caa gat atc att ctg agg ctg aca cat gtt aaa act gga gga aaa   672
Ile Gln Asp Ile Ile Leu Arg Leu Thr His Val Lys Thr Gly Gly Lys
            130                 135                 140

atc tcc ttg cgg aaa gca agg tat cac act tta acc aaa atc tgt gcg   720
Ile Ser Leu Arg Lys Ala Arg Tyr His Thr Leu Thr Lys Ile Cys Ala
        145                 150                 155

gtg caa gag ata atc gaa gac tgc atg aaa aag cag cct tcc ctg ccg   768
Val Gln Glu Ile Ile Glu Asp Cys Met Lys Lys Gln Pro Ser Leu Pro
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BNSDOCID <WO__0014106A1_I_>

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ctt tcc gag gat gca cat cct tcc gtt gcc aaa atc aac ttc gtg atg   816
Leu Ser Glu Asp Ala His Pro Ser Val Ala Lys Ile Asn Phe Val Met
175                 180                 185                 190

tgt gag gtg aac aag gcc cga ggg gtc ctg att gca ctt ctg atg ggt   864
Cys Glu Val Asn Lys Ala Arg Gly Val Leu Ile Ala Leu Leu Met Gly
                195                 200                 205

gtg aac aac aat gag acc tgc agg cac tta tcc tgt gtg ctc tcg ggg   912
Val Asn Asn Asn Glu Thr Cys Arg His Leu Ser Cys Val Leu Ser Gly
            210                 215                 220

ctg atc gct gac ctg gat gct cta gat gtg tgc ggc cgg aca gaa atc   960
Leu Ile Ala Asp Leu Asp Ala Leu Asp Val Cys Gly Arg Thr Glu Ile
        225                 230                 235

aga aat tat cgg agg gag gta gta gaa gat atc aac aaa tta ttg aaa   1008
Arg Asn Tyr Arg Arg Glu Val Val Glu Asp Ile Asn Lys Leu Leu Lys
    240                 245                 250

tat ctg gat ttg gaa gag gaa gca gac aca act aaa gca ttt gac ctg   1056
Tyr Leu Asp Leu Glu Glu Glu Ala Asp Thr Thr Lys Ala Phe Asp Leu
255                 260                 265                 270

aga cag aat cat tcc att tta aaa ata gaa aag gtc ctc aag aga atg   1104
Arg Gln Asn His Ser Ile Leu Lys Ile Glu Lys Val Leu Lys Arg Met
                275                 280                 285

aga gaa ata aaa aat gaa ctt ctc caa gca caa aac cct tct gaa ttg   1152
Arg Glu Ile Lys Asn Glu Leu Leu Gln Ala Gln Asn Pro Ser Glu Leu
            290                 295                 300

tac ctg agc tcc aaa aca gaa ttg cag ggt tta att gga cag ttg gat   1200
Tyr Leu Ser Ser Lys Thr Glu Leu Gln Gly Leu Ile Gly Gln Leu Asp
        305                 310                 315

gag gta agt ctt gaa aaa aac ccc tgc atc cgg gaa gcc agg aga aga   1248
Glu Val Ser Leu Glu Lys Asn Pro Cys Ile Arg Glu Ala Arg Arg Arg
    320                 325                 330

gca gtg atc gag gtg caa act ctg atc aca tat att gac ttg aag gag   1296
Ala Val Ile Glu Val Gln Thr Leu Ile Thr Tyr Ile Asp Leu Lys Glu
335                 340                 345                 350

gcc ctt gag aaa aga aag ctg ttt gct tgt gag gag cac cca tcc cat   1344
Ala Leu Glu Lys Arg Lys Leu Phe Ala Cys Glu Glu His Pro Ser His
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aaa gcc gtc tgg aac gtc ctt gga aac ttg tct gag atc cag gga gaa   1392
Lys Ala Val Trp Asn Val Leu Gly Asn Leu Ser Glu Ile Gln Gly Glu
            370                 375                 380

gtt ctt tca ttt gat gga aat cga acc gat aag aac tac atc cgg ctg   1440
Val Leu Ser Phe Asp Gly Asn Arg Thr Asp Lys Asn Tyr Ile Arg Leu
        385                 390                 395

gaa gag ctg ctc acc aag cag ctg cta gcc ctg gat gct gtt gat ccg   1488
Glu Glu Leu Leu Thr Lys Gln Leu Leu Ala Leu Asp Ala Val Asp Pro
    400                 405                 410

cag gga gaa gag aag tgt aag gct gcc agg aaa caa gct gtg agg ctt   1536
Gln Gly Glu Glu Lys Cys Lys Ala Ala Arg Lys Gln Ala Val Arg Leu
415                 420                 425                 430

gcg cag aat att ctc agc tat ctc gac ctg aaa tct gat gaa tgg gag   1584
Ala Gln Asn Ile Leu Ser Tyr Leu Asp Leu Lys Ser Asp Glu Trp Glu
                435                 440                 445

tac tga aataccagag atctcacttt tgatactgtt ttgcacttca tatgtgcttc    1640
Tyr

tatgtataga gagctttcag ttcattgatt tatacgtgca tatttcagtc tcagtattta 1700

tgattgaagc aaattctatt cagtatctgc tgcttttgat gttgcaagac aaatatcatt 1760

acagcacgtt aacttttcca ttcggatcat tatctgtatg atgtggtgtg gtttgtttgg 1820

tttgtccttt tttttgcgtt tttaatcaga aaacaaaata gaggcagctt ttgtagattt 1880

taaatgggtt gtgcaagcat taaaatgcag gtctttcaga atctagaact aggcataacc 1940

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tcaaacacaa gcagtacatg ttctgtttca ttatgctcga tagaaggctt ttttttcact 2060

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BNSDOCID <WO 0014106A1 >

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gtaacccaga gggaccaggc cttcctaggt tttctaggca gtcagctgtt aaccactcac 2660

ttagtaaatg tcataactac acctgctcca ggaccaatca gtgaaacctg ctcggaatta 2720

aaggcttcct ctgggtgcct gctgaacaac tgagctcatg tcatgggcat gtggtggttt 2780

ctctgttgcc tgaaagagcc attaaagtca gtcgtgcgtg aagcatctct cttctaaagg 2840

atgtgtattt ccataaatgc tttctgagga tccggtacaa aatgatttcc caaagttctg 2900

aagtgccttg agaacatgtg ggtccgagtg ttataacaga ctcctccccc gggtcacctt 2960

ttgcctggtc atcctgttag agtacatctt tggaaatcca gggtaatatt ctctttcaga 3020

gatgctcatt gtgtaactct gtgtagggag atagtcactt taaacagctc aaagtagcta 3080

gctaaaggag tagccttaaa tacctaaaag atgacagaag catagccctt aacaaatctt 3140

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aatgttctag aatcgctgga cggtggggtc agagggcagt cggtatttag gccgtgagct 3260

tcccatacta ctgcaggtcc aactcctggc aaccgcgggc tcaaggcagg tcattggaat 3320

ccacgttttg gccacagtag ttgtaggatt gcttttctgt atcataattt tagaatgctc 3380

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BNSDOCID <WO 0014106A1 I >

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BNSDOCID <WO 0014106A1 >

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21053

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :07N 21/02; C07K 1/00

US CL :530/387.1, 350; 435/6, 7/1; 536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/387.1, 350; 435/6, 7/1; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,652,223 A (KOHN ET AL) 29 July 1997(29/7/97) see entire document.	2-5, 14, 32-34
X	Database Genbank-EST, National Center for Biotech. Info., Accession No. AA693697, HILLIER, L. ET AL. 'WashU-NCI human EST Project,' 16 December 1997, see entire reference.	2
X	Database Genbank-EST, National Center for Biotech. Info., Accession No. AA456862, NCI_CGAP, 'National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index,' 15 August 1997, see entire reference.	2,4

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 24 NOVEMBER 1999	Date of mailing of the international search report 19 JAN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHEELA J. HUFF Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

BNSDOCID <WO 0014106A1 1 >

INTERNATIONAL SEARCH REPORT

International application No
PCT/US99/21053

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1, 13, 24, 25
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

No meaningful search could be carried out because no limitations could be placed on the sequence

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest

☐ No protest accompanied the payment of additional search fees

BNSDOCID <WO 0014106A1 I_>

INTERNATIONAL SEARCH REPORT

International application No
PCT/US99/21053

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database Genbank, National Center for Biotech. Info., Accession No. G29287, MYERS, R.M., 04 October 1996, see entire reference.	2,4
X	Database Genbank, National Center for Biotech. Info., Accession No. G06974, HUDSON, T., "Whitehead Institute.MIT Center for Genome Research,'19 October 1995, see entire reference.	2,4
X	Database Genseq, Derwent, Alexandria, Virginia, Accession No. V81267, OTSUKA PHARM CO LTD, 'New Bcl-2 interaction prrtein gene (Bis)- useful for elucidation of the molecular mechanism of apoptosis, and in diagnosis, prevention and treatment of diseases,' 15 December 1998 see enire reference.	2-5
X	Database, Geneseq, Derwent, Alexandria, Virginia, Accession No. T19051, MATSUBARA ET AL., "Identifying gene signatures in 3'-directed human cDNA library,' 01 June 1995, see entire reference.	2,4
X	Database Geneseq, Derwent, Alexandria, Virginia, Accession No. Q90296, LA JOLLA CANCER RES FOUN. 'Human Bcl-2-associated protein BAG-1 cDNA,'18 May 1995 see entire reference.	2-5,14

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BNSDOCID <WO 0014106A1 I >

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
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(54) Title: NOVEL BAG PROTEINS AND NUCLEIC ACID MOLECULES ENCODING THEM

(57) Abstract

The present invention provides a family of BAG–1 related proteins from humans (BAG–1L, BAG–1, BAG–2, BAG–3, BAG–4 and BAG–5), the invertebrate *C. elegans* (BAG–1, BAG–2) and the fission yeast *S. pombe* (BAG–1A, BAG–1B) and the nucleic acid molecules that encode them.

*(Referred to in PCT Gazette No. 25/2000, Section II)

BNSDOCID <WO_0014106A1_IA>

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BNSDOCID <WO 0014106A1 IA>

NOVEL BAG PROTEINS AND NUCLEIC ACID MOLECULES ENCODING THEM

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY-SPONSORED RESEARCH AND DEVELOPMENT

This invention was made with government support under grant number CA-67329 awarded by the National Institutes of Health. The United States Government has certain rights in this invention.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

This invention relates generally to the fields of molecular biology and molecular medicine and more specifically to a novel family of proteins that can regulate protein folding. The functions of these proteins are potentially diverse, including promoting tumor cell growth and metastasis.

BACKGROUND INFORMATION

The Hsc70/Hsp70-family of molecular chaperones participate in protein folding reactions, controlling protein bioactivity, degradation, complex assembly/disassembly, and translocation across membranes. These proteins interact with hydrophobic regions within target proteins via a carboxyl (C)-terminal peptide binding domain, with substrate binding and release being controlled by the N-terminal ATP-binding domain of Hsc70/Hsp70. Hsc70/Hsp70-assisted folding reactions are accomplished by repeated cycles of peptide binding, refolding, and release,

which are coupled to ATP hydrolysis by the ATP-binding domain (ATPase) of Hsc70/Hsp70 and by subsequent nucleotide exchange. The chaperone activity of mammalian Hsc70/Hsp70 is regulated by partner proteins that either modulate the peptide binding cycle or that target the actions of these chaperones to specific proteins and subcellular compartments. DnaJ-family proteins (Hdj-1/Hsp40; Hdj-2; Hdj-3) stimulate the ATPase activity of Hsc70/Hsp70, resulting in the ADP-bound state which binds tightly to peptide substrates. The Hip protein collaborates with Hsc70/Hsp70 and DnaJ homologues in stimulating ATP hydrolysis, and thus also stabilize Hsc70/Hsp70 complexes with substrate polypeptides, whereas the Hop protein may provide co-chaperone functions through interactions with the C-terminal peptide binding domain.

The Bcl-2 associated athanogene-1 (bag-1) is named from the Greek word *athanos*, which refers to anti-cell death. BAG-1 was previously referred to as Bcl-2-associated protein-1 (BAP-1) in U.S. Patent No. 5,539,094 issued July 23, 1996, which is incorporated herein by reference. In this earlier patent, BAG-1 is described as a portion of the human BAG-1 protein, absent the N-terminal amino acids 1 to 85. In addition, a human protein essentially identical to human BAG-1 was described by Zeiner and Gehring, (*Proc. Natl. Acad. Sci., USA* **92**:11465-11469 (1995)). Subsequent to the issuance of U.S. Patent 5,539,094 the N-terminal amino acid sequence from 1 to 85 of human BAG-1 was reported.

BAG-1 and its longer isoforms BAG-1M (Rap46) and BAG-1L are recently described Hsc70/Hsp70-regulating proteins. BAG-1 competes with Hip for binding to the Hsc70/Hsp70 ATPase domain and promotes substrate release. BAG-1 also reportedly stimulates Hsc70-mediated ATP

hydrolysis by accelerating ADP/ATP exchange, analogous to the prokaryotic GrpE nucleotide exchange protein of the bacterial Hsc70 homologue, DnaK. Gene transfection studies indicate that BAG-1 proteins can influence a wide variety of cellular phenotypes through their interactions with Hsc70/Hsp70, including increasing resistance to apoptosis, promoting cell proliferation, enhancing tumor cell migration and metastasis, and altering transcriptional activity of steroid hormone receptors.

Despite the notable progress in the art, there remains an unmet need for the further identification and isolation of additional homologous BAG protein species, and the nucleic acid molecules and/or nucleotide sequences that encode them. Such species would provide additional means by which the identity and composition of the BAG domain, that is, the portion of the protein that is influencing or modulating protein folding, could be identified. In addition, such species would be useful for identifying agents that modulate apoptosis as candidates for therapeutic agents, in particular, anticancer agents. The present invention satisfies these need, as well as providing substantial related advantages.

SUMMARY OF THE INVENTION

The present invention provides a family of BAG-1 related proteins from humans [BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO: 4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22) and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24)] , the invertebrate C.*elegans* [BAG-1 (SEQ ID NO:12), BAG-2 (SEQ ID NO:14)] and the fission yeast S.*pombe* [BAG-1A (SEQ ID NO:16), BAG-1B (SEQ ID NO:18)] and the nucleic acid molecules that encode them.

Another aspect of the present invention provides an amino acid sequence present in the family of BAG-1 related proteins, that modulates Hsc70/Hsp70 chaperone activity, that is, the BAG domain.

Another aspect of the present invention provides novel polypeptide and nucleic acid compositions and methods useful in modulating Hsc70/Hsp70 chaperone activity.

Another aspect of the present invention is directed to methods for detecting agents that modulate the binding of the BAG family of proteins, such as BAG-1 (beginning at residue 116 of SEQ ID NO:2), and related proteins with the Hsc70/Hsp70 Family of proteins or with other proteins that may interact with the BAG-Family proteins.

Still another aspect of the present invention is directed to methods for detecting agents that induce the dissociation of a bound complex formed by the association of BAG-Family proteins with Hsc70/Hsp70 Family molecule chaperones or other proteins.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the full length cDNA sequence for human BAG-1 (SEQ ID NO:1) protein with the corresponding amino acid sequence (SEQ ID NO:2). Within the full length sequence are included the overlapping sub-sequences of BAG-1 (beginning at nucleotide 391), BAG-1M [beginning at nucleotide 260 of (SEQ ID NO:2)], and BAG-1L [beginning at nucleotide 46 of (SEQ ID NO:2)].

BNSDOCID <WO 0014106A1 IA>

Figures 2A and 2B combined shows the full length cDNA sequence (SEQ ID NO:3) aligned with the corresponding amino acid residues for human BAG-2 protein (SEQ ID NO:4).

Figure 3 shows a cDNA sequence (SEQ ID NO:5) aligned with the corresponding amino acid residues for human BAG-3 protein (SEQ ID NO:6).

Figure 4 shows the a cDNA sequence (SEQ ID NO:7) aligned with the corresponding amino acid residues for human BAG-4 protein (SEQ ID NO:8).

Figure 5 shows a cDNA sequence (SEQ ID NO:9) aligned with the corresponding amino acid residues for human BAG-5 protein (SEQ ID NO:10).

Figure 6A shows the full length cDNA sequence for *C. elegans* BAG-1 protein (SEQ ID NO:11).

Figure 6B shows the 210 amino acid sequence for *C. elegans* BAG-1 protein (SEQ ID NO:12).

Figure 7A shows the full length cDNA sequence for *C. elegans* BAG-2 protein (SEQ ID NO:13).

Figure 7B shows the 458 amino acid sequence for *C. elegans* BAG-2 protein (SEQ ID NO:14).

Figure 8A shows the full length cDNA sequence for *S. pombe* BAG-1A protein (SEQ ID NO:15).

Figure 8B shows the 195 amino acid sequence for *S. pombe* BAG-1A protein (SEQ ID NO:16).

Figure 9A shows the full length cDNA sequence for *S. pombe* BAG-1B protein (SEQ ID NO:17).

Figure 9B shows the 206 amino acid sequence for *S. pombe* BAG-1B protein (SEQ ID NO:18).

Figure 10 shows the topologies of the BAG-family proteins; human BAG proteins, BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), BAG-4 (SEQ ID NO:8), BAG-5 (SEQ ID NO:10); *S.pombe* BAG-1A (SEQ ID NO:16)and BAG-1B (SEQ ID NO:18); and *C. elegans* BAG-1 (SEQ ID NO:12)and BAG-2 (SEQ ID NO:14). (A) The relative positions of the BAG domains are shown in black, ubiquitin-like regions are represented in gray, WW domain are represented in strips. Nucleoplasmin-like nuclear localization sequence are also shown. (B) The amino acid sequences of the BAG domain for human BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), BAG-4 (SEQ ID NO:8), BAG-5 (SEQ ID NO:10), *S.pombe* BAG-1A (SEQ ID NO:16)and BAG-1B (SEQ ID NO:18), and *C. elegans* BAG-1 (SEQ ID NO:12)and BAG-2 (SEQ ID NO:14) are aligned demonstrating their homology. Black and gray shading represent identical and similar amino acids, respectively.

Figure 11 shows assays demonstrating the interaction of BAG-family proteins with Hsc70/ATPase. (A) Two-hybrid assays using yeast expressing the indicated fusion proteins. Blue color indicates a positive interaction, resulting in activation of the *lacZ* reporter gene. (B) *In vitro* protein assays using GST-fusion proteins and ^{35}S-labeled *in vitro* translated proteins. (C) Co-immunoprecipitation assays using anti-Flag or IgG1 control antibodies and lysates from 293T cells expressing Flag-tagged BAG-1 (beginning at residue 116 of SEQ ID

NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), Daxx, or Apaf-1.

Figure 12 shows surface plasmon resonance analysis of BAG-family protein interactions with Hsc70/ATPase. (A) SDS-PAGE analysis of purified recombinant proteins. (B) Representative SPR results of biosensor chips containing immobilized BAG proteins with and without maximally bound Hsc70/ATPase.

Figure 13 shows representative SPR results for biosensor chips containing immobilized BAG-1 (beginning at residue 116 at SEQ ID NO:2), BAG-1(ΔC), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) proteins. Hsc70/ATPase was flowed over the chips (arrow/left) until maximal binding was reached (response units), then flow was continued without Hsc70/ATPase (arrow/right). For BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6), Hsc70 was injected at 0.0175, 0.035, 0.07, 0.14, and 0.28 μM.

Figure 14 shows BAG-family protein modulation of Hsc70 chaperone activity. (A) Protein refolding assay of chemically-denatured luciferase by Hsc70 plus DnaJ in the absence or presence of BAG and BAG-mutant proteins. (B) Concentration-dependent inhibition of Hsc70-mediated protein refolding by BAG-family proteins [BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6)] but not by BAG-mutant (BAG-1 (ΔC). (C) Hsc70/Hsp40-mediated refolding of heat-denatured luciferase was assayed in the presence of (black bars) or absence of (striped bars) of 1.8 μM Hip, with (lanes 3-10) or without (lanes 1,2) various BAG-family proteins (1.8μM) as indicated (mean ±SE; n=3). A control (CNTL) is shown (lane 1) in which Hsc70 was replaced with an equivalent amount of BSA.

BNSDOCID <WO 0014106A1 A>

Figure 15A shows an expanded cDNA sequence for human BAG-3 protein (SEQ ID NO:19).

Figure 15B shows the corresponding amino acid residues for the human BAG-3 protein (SEQ ID NO:20) of Figure 15A.

Figure 15C shows the expanded cDNA sequence (SEQ ID NO:19) aligned with the corresponding amino acid residues for human BAG-3 protein of Figure 15A (SEQ ID NO:20).

Figure 16A shows an expanded cDNA sequence for human BAG-4 protein (SEQ ID NO:21).

Figure 16B shows the corresponding amino acid residues for the human BAG-4 protein of Figure 16A (SEQ ID NO:22).

Figure 16C shows the expanded cDNA sequence (SEQ ID NO:21) aligned with the corresponding amino acid residues for human BAG-4 protein of Figure 16A (SEQ ID NO:22).

Figure 17A shows an expanded cDNA sequence for human BAG-5 protein (SEQ ID NO:23).

Figure 17B shows the corresponding amino acid residues for the human BAG-5 protein of Figure 17A (SEQ ID NO:24).

Figure 17C shows the expanded cDNA sequence (SEQ ID NO:23) aligned with the corresponding amino acid residues for human BAG-5 protein of Figure 17A (SEQ ID NO:24).

Figure 18 shows the topologies of the BAG-family proteins; human BAG proteins, BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), expanded BAG-3 (SEQ ID NO:20), expanded BAG-4 (SEQ ID NO:22), expanded BAG-5 (SEQ ID NO:24); *S.pombe* BAG-1A (SEQ ID NO:16)and BAG-1B (SEQ ID NO:18); and *C. elegans* BAG-1 (SEQ ID NO:12)and BAG-2 (SEQ ID NO:14). The relative positions of the BAG domains are shown in black, ubiquitin-like regions are represented in gray, WW domain are represented in strips. Nucleoplasmin-like nuclear localization sequence are also shown.

Definitions

The term "apoptosis", as used herein, refers to the process of programmed cell death, although not all programmed cell deaths occur through apoptosis, as used herein, "apoptosis" and "programmed cell death" are used interchangeably.

The term "tumor cell proliferation", as used herein refers to the ability of tumor cells to grow and thus expand a tumor mass.

The term "cell migration", as used herein refers to the role cell motility plays in the invasion and potentially metastasis by tumor cells.

The term "metastasis", as used herein refers to the spread of a disease process from one part of the body to another, as in the appearance of neoplasms in parts of the body remote from the site of the primary tumor; results in dissemination of tumor cells by the lymphatics or blood vessels or by direct extension through serious cavitites or subarachnoid or other spaces.

The term "steroid hormone receptor function", as used herein refers to physiological, cellular and molecular functioning of receptors sites that bind with steroid hormones.

The term "substantially purified", as used herein, refers to nucleic acid or amino acid sequence that are removed from their natural environment, isolated or separated, and are at least 60% free, preferably 75% free, and most preferably 90% free from other components with which they are naturally associated.

"Nucleic acid molecule" as used herein refers to an oligonucleotide, nucleotide, or polynucleotide, and fragments or portions thereof, and to DNA or RNA of genomic or synthetic origin which may be single or double stranded, and represent the sense or antisense strand.

"Hybridization", as used herein, refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The terms "complementary" or "complementarity", as used herein, refer to the natural binding of polynucleotides under permissive salt and temperature conditions by base-pairing. For example, the sequence "A-G-T binds to the complementary sequence "T-C-A".

The term "homology", as used herein, refers to a degree of complementarity. There may be partial homology or complete homology (i.e., identity). A partially complementary sequence is one that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid and is referred to using the functional term "substantially homologous." The inhibition of

hybridization of the completely complementary sequence to the target sequence may be examined using a hybridzation assay (Southern or northern blot, solution hybridization and the like) under conditions of low stringency. A substantially homologous sequence or probe will compete for and inhibit the binding (i.e., the hybridization) of a completely homologous sequence or probe to the target sequence under conditions of low stringency.

The term "antisense", as used herein, refers to nucleotide sequences which are commplementary to a specific DNA or RNA sequence. The term "antisense strand" is used in reference to a nucleic acid strand that is complementary to the "sense" strand. Antisense molecules may be produced by any method, including synthesis by ligating the gene(s) of interest in a reverse orientation to a viral promoter which permits the synthesis of a complementary strand. Once introduced into a cell, this transcribed strand combines with natural sequences produced by the cell to form duplexes. These duplexes then block either the further transcription or translation. In this manner, mutant phenotypes may be generated. The designation "negative" is sometimes used in reference to the antisense, and "positive" is sometimes used in reference to the sense strand.

"Amino acid sequence" as used herein refers to an oligopeptide, peptide, polypeptide, or protein sequence, and fragments or portions thereof, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited herein this term excludes an amino acid sequence of a naturally occurring protein. "Amino acid sequence", "polypeptide" or "protein" are not meant to limit the amino acid sequence to the complete, native amino acid sequence associated with the recited protein molecule.

The term "functional fragments" or "fragments", as used herein, with regard to a protein refers to portions of that protein that are capable of exhibiting or carrying out the activity exhibited by the protein as a whole. The portions may range in size from three amino acid residues to the entire amino acid sequence minus one amino acid. For example, a protein "comprising at least a functional fragment of the amino acid sequence of SEQ ID NO:1", encompasses the full-length of the protein of SEQ ID NO:1 and portions thereof.

A "derivative" of a BAG protein, as used herein, refers to an amino acid sequence that is alterd by one or more amino acids. The derivative may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties, e.g., substitution of an apolar amino acid with another apolar amino acid (such as replacement of leucine with isoleucine). The derivative may also have "nonconservative" changes, wherein a substituted amino acid has different but sufficiently similar structural or chemical properties that permits such a substitution without adversely effecting the desired biological activity, e.g., replacement of an amino acid with an uncharged polar R group with an amino acid with an apolar R group (such as replacement of glycine with tryptophan), or alternatively replacement of an amino acid with a charged R group with an amino acid with an uncharged Polar R group (such as replacement of lysine with asparagine).

Amino Acids - Apolar R Groups

Amino Acid	Radical	Abbreviations	
		3-Letter	1-Letter
alanine	methyl	ala	A
valine	2-propyl	aal	V
leucine	2-methylpropyl	leu	L
isoleucine	2-butyl	ile	I
proline	propyl* - cyclized	pro	P
phenylalanine	benzyl	phe	F
trytophan	3-indolylmethl	tyr	W
methionine	methylthioethyl	met	M

Amino Acids - Uncharged Polar R Groups

Amino Acid	Radical	Abbreviations	
		3-Letter	1-Letter
glycine	H	gly	G
serine	hydroxymethyl	ser	S
threonine	1-hydroxyethyl	thr	T
cysteine	thiolmethyl	cys	C
tyrosine	4-hydroxyphenylmethyl	tyr	Y
asparagine	aminocarbonylmethyl	asn	N
glutamine	aminocarbonylethyl	gln	Q

Amino Acids - Charged R Groups

Amino Acid	Radical	Abbreviations	
		3-Letter	1-Letter
aspartic acid	carboxymethyl	asp	D
glutamic acid	carboxyethyl	glu	E
lysine	4-aminobutyl	lys	K
arginine	3-guanylpropyl	arg	R
histidine	4-imidazoylmethyl	his	H

Similar minor modifications may also include amino acids deletions or insertions or both. Guidance in determining which amino acid residues may be modified as indicated above without abolishing the desired biological functionality may be determined using computer programs well known in the art, for example, DNASTAR software. In addition, the derivative may also result from chemical modifications to the encoded polypeptide, including but not limited to the following, replacement of hydrogen by an alkyl, acyl, or amino group; esterification of a carboxyl group with a suitable alkyl or aryl moiety; alkylation of a hydroxyl group to form an ether derivative. Further a derivative may also result from the substitution of a L-configuration amino acid with its corresponding D-configuration counterpart.

The term "mimetic", as used herein, refers to a molecule, the structure of which is developed from knowledge of the structure of a protein/polypeptide or portions thereof (such as BAG-1) and, as such, is able to effect some or all of the actions of BAG-1 protein.

"Peptide nucleic acid", as used herein, refers to a molecule which comprises an oligomer to which an amino acid residue, such as lysine, and an amino group have been added. These small molecules, also designated anti-gene agents, stop transcript elongation by binding to their complementary strand of nucleic acid (Nielsen, P.E. et al., *Anticancer Drug Des.* 8:53-63 (1993)).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a family of BAG-1 related proteins from humans [BAG-1L (SEQ ID NO:2), BAG-1S beginning at residue 116 of SEQ ID NO:2, BAG-2 (SEQ ID

BNSDOCID <WO 0014106A1 IA>

NO:4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO: 8) and (SEQ ID NO:22) and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24)], the invertebrate *C.elegans* [BAG-1 (SEQ ID NO:12), BAG-2 (SEQ ID NO:14)] and the fission yeast *S.pombe* [BAG-1A (SEQ ID NO:16), BAG-1B (SEQ ID NO:18)], specifically the full length amino acid sequences comprising human BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), and BAG-2 (SEQ ID NO:4) *C. elegans* BAG-1 (SEQ ID NO:12), and BAG-2 (SEQ ID NO:14), and *S.pombe* BAG-1A (SEQ ID NO:16) and BAG-1B (SEQ ID NO:18); and partial sequences comprising human BAG-3 (SEQ ID NO: 6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22), and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24) and functional fragments thereof. In particular, the invention provides the amino acid sequences comprising human BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22), and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24) proteins.

Another aspect of the present invention provides the nucleic molecule and nucleotide sequences that encode the family of BAG-1 related proteins from humans [BAG-1 (SEQ ID NO:1), BAG-2 (SEQ ID NO:3), BAG-3 (SEQ ID NO:5) and (SEQ ID NO:19), BAG-4 (SEQ ID NO:7) and (SEQ ID NO:21) and BAG-5 (SEQ ID NO:9) and (SEQ ID NO:23)], the invertebrate *C.elegans* [BAG-1 (SEQ ID NO:11), BAG-2(SEQ ID NO:13)] and the fission yeast *S.pombe* [BAG-1A (SEQ ID NO:15), BAG-1B (SEQ ID NO:17)].

BAG-1L (SEQ ID NO:2) is a multifunctional protein that blocks apoptosis, promotes tumor cell metastasis, and contributes to factor-independent and p53-resistant cell growth. BAG-1L (SEQ ID NO:2) interacts with several types of proteins, including Bcl-2, some tyrosine kinase growth

factor receptors, steroid hormone receptors, and the p53-induced cell cycle regulator Siah-1A.

BAG-1 is a regulator of Hsc70/Hsp70 family molecular chaperones. A carboxyl-terminal domain in this protein binds tightly to the ATPase domains of Hsc70 and Hsp70 (K_D = 1 nM) (Zeiner, M., Gebauer, M., and Gehring, U., *EMBO J.* ***16:*** 5483-5490, (1997)). BAG-1 modulates the activity of these molecular chaperones, acting as an apparent functional antagonist of the Hsp70/Hsc70-associated protein Hip (3-5)(Höhfeld, J. and Jentsch, S., *EMBO J.* ***16:*** 6209-6216, (1997); Takayama, S., Bimston, D. N., Matsuzawa, S., Freeman, B. C., Aime-Sempe, C., Xie, Z., Morimoto, R. J., and Reed, J. C., *EMBO J.* ***16:*** 4887-96, (1997); Zeiner, M., Gebauer, M., and Gehring, U., *EMBO J.* ***16:*** 5483-5490, (1997)). In general, protein refolding is accomplished by Hsp70/Hsc70 through repeated cycles of target peptide binding and release, coupled to ATP hydrolysis (Ellis, R., *Curr Biol.* **7**: R531-R533, (1997)). BAG-1 appears to promote substrate release, whereas Hip stabilizes Hsp70/Hsc70 complex formation with target peptides (Höhfeld, J., Minami, Y., and Hartl, F.-U., *Cell.* **83**: 589-598, (1995)). Since each substrate interaction with Hsc70/Hsp70 is unique in terms of the optimal length of time the protein target should remain complexed with Hsc70/Hsp70 for achieving new conformations, the net effect of BAG-1 can be either enhancement or inhibition of the refolding reaction.

The 70kd heat shock family proteins (Hsp70/Hsc70) are essential to a variety of cellular processes and have been implicated in cancer, yet it is unclear how these proteins are regulated *in vivo*. A variety of co-chaperones have been identified which may target Hsp70/Hsc70 to different subcellular compartments or promote their

BNSDOCID <WO 0014106A1 IA>

interactions with specific protein or protein complexes. BAG-1 appears to represent a novel Hsp70/Hsc70 regulator which differs functionally from all other mammalian co-chaperones identified to date, such as members of the DnaJ-, Hip-, Hop-, and cyclophilin-families of proteins.

Another aspect of the present invention provides the amino acid sequence of a binding domain of about 40 to 55 amino acids that bind the a Hsc70/Hsp70 ATPase domain. The BAG domain is situated near the C-terminus, and the ubiquitin-like domains are situated near the N-terminus.

The BAG family of proteins of the present invention contain a common conserved C-terminal domain (the "BAG" domain) that facilitates binding to the ATPase domain of Hsp70/Hsc70. The carboxyl-terminal domain of BAG-1 binds to the ATPase domain of Hsc70/Hsp70 and regulates its chaperone function by acting as a ADP-ATP exchange factor. Other domains of BAG-1 mediate interactions with proteins such as Bcl-2 and retinoic acid receptors (RARs), allowing BAG-1 to target Hsc70/Hsp70 to other proteins, presumably modulating their function by changing their conformations.

Human BAG-1 was previously shown to inhibit Hsc70/Hsp70 dependent refolding of denatured protein substrates *in vitro* (S. Takayama, et al., *EMBO J* **16**, 4887-96 (1997); M. Zeiner, M. Gebauer, U. Gehring, *EMBO J.* **16**, 5483-5490 (1997); and J. Höhfeld, S. Jentsch, *EMBO J.* **16**, 6209-6216 (1997)). In Example III, Part A the effects of recombinant human BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) were compared using *in vitro* protein refolding assays similar to those employed previously for assessing BAG-1. The study showed that addition of equimolar amounts of each of the recombinant proteins to Hsc70 resulted in significant inhibition of luciferase refolding, with BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) showing somewhat

BNSDOCID <WO _ 0014106A1 IA>

greater inhibitor activity than BAG-1 (Figure 4A). In a separate luciferase folding study BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) once again displayed inhibition of luciferase refolding, however in this study varying amounts of BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) were added relative to Hsc70 which resulting in concentration-dependent inhibition of Hsc70 chaperone activity, i.e., luciferase folding (Example III Part A). Additional follow on studies using the same experimental protocols as the previous studies, as taught in Example IIA, have shown that BAG-4 (SEQ ID NO:22) also undergoes association with Hsc70/ATPase.

Yet another aspect of the present invention provides a nucleotide sequence having at least about 15 nucleotides and, generally, about 25 nucleotides, preferably about 35 nucleotides, more preferably about 45 nucleotides, and most preferably about 55 nucleotides that can hybridize or is complementary under relatively stringent conditions to a portion of the nucleic acid sequences shown in Figures 1-9 and Figures 15-17, in particular the BAG domain as shown in in Figure 1B, e.g., nucleotides 552-593 of human BAG-3, or nucleotides 167-221 of human BAG-4.

Yet another aspect of the present invention provides a compound of the formula,

$$R^N\text{-}R^1X^1R^2X^2R^3X^3R^4X^4R^5X^5R^6X^6R^7X^7X^8R^9X^9R^{10}X^{10}R^{11}X^{11}\text{-}R^C$$

wherein,

R^N is a group of 1 to 552 independently selected amino acids;

R^1 is a group of 3 independently selected amino acids;

BNSDOCID <WO 0014106A1 IA>

X^1 is an amino acid with a charged or uncharged R group, such as aspartic acid, glutamic acid, asparagine, or glutamine;

R^2 is a group of 7 independently selected amino acids;

X^2 is an amino acid with a charged R group, such as glutamic acid;

R^3 is a group of 5 independently selected amino acids;

X^3 is an amino acid with an apolar R group, such as leucine, methionine, or isoleucine;

R^4 is a group of 3 independently selected amino acids;

X^4 is an amino acid with charged R group, such as aspartic acid or glutamine acid;

R^5 is a single independently selected amino acid;

X^5 is an amino acid with apolar or uncharged R group, such as leucine, valine, methionine, alanine or threonine;

R^6 is a group of 15 independently selected amino acids;

X^6 is an amino acid with a charged or uncharged R group, such as arginine, lysine, glutamine or aspartic acid;

R^7 is a group of 2 independently selected amino acids;

X^7 is an amino acid with a charged R group, such as arginine;

X^8 is an amino acid with a charged R group, such as arginine or lysine;

R^9 is a group of 2 independently selected amino acids;

X^9 is an amino acid with an apolar R group, such as valine;

R^{10} is a group of 3 independently selected amino acids;

BNSDOCID <WO 0014106A1 IA>

X^{10} is an amino acid with an uncharged R group, such as glutamine;

R^{11} is a group of 2 independently selected amino acids;

X^{11} is an amino acid with an apolar R group, such as leucine; and

R^{C} is a group of 1 to 100 independently selected amino acids.

A nucleotide sequence of at least about 15 nucleotides and, generally, about 25 nucleotides, preferably about 35 nucleotides, more preferably about 45 nucleotides, and most preferably about 55 nucleotides can be useful, for example, as a primer for the polymerase chain reaction (PCR) or other similar reaction mediated by a polymerase such as a DNA or RNA polymerase (see PCR Protocols: A guide to methods and applications, ed. Innis et al. (Academic Press, Inc., 1990), which is incorporated herein by reference; see, for example, pages 40-41). In addition, such a nucleotide sequence of the invention can be useful as a probe in a hybridization reaction such as Southern or northern blot analysis or in a binding assay such as a gel shift assay.

A nucleotide sequence of the invention can be particularly useful as an antisense molecule, which can be DNA or RNA and can be targeted to all or a portion of the 5'-untranslated region or of the 5'-translated region of a bag-1 nucleic acid sequence in a cell. For example, an antisense molecule can be directed to at least a portion of the sequence shown as the BAG domain in Figure 1A, e.g., nucleotides 272-319 of human BAG-1L (SEQ ID NO:1), or nucleotides 79-147 of human BAG-5 (SEQ ID NO:9). Since the 5'-region of a nucleic acid contains elements involved in the control of expression of an encoded protein, an antisense molecule directed to the 5'-region of a nucleic

BNSDOCID <WO 0014106A1 IA>

acid molecule can affect the levels of protein expressed in a cell.

A nucleotide sequence of the invention also can be useful as a probe to identify a genetic defect due a mutation of a gene encoding a BAG protein in a cell. Such a genetic defect can lead to aberrant expression of a BAG protein in the cell or to expression of an aberrant BAG protein, which does not properly associate with a Bcl-2-related protein or Hsc70/Hsp70 protein in the cell. As a result, a genetic defect in a gene encoding, for example, human BAG-1 can result in a pathology characterized by increased or decreased levels in protein folding.

Further a nucleotide compound or composition as taught in the present invention can be synthesized using routine methods or can be purchased from a commercial source. In addition, a population of such nucleotide sequences can be prepared by restriction endonuclease or mild DNAse digestion of a nucleic acid molecule that contains nucleotides as shown in the nucleotide sequences shown in Figures 1-9 and Figures 15-17 that encodes the amino acids sequences also shown in Figures 1-9 and Figures 15-17. Methods for preparing and using such nucleotide sequences, for example, as hybridization probes to screen a library for homologous nucleic acid molecules are well known in the art (see, for example, Sambrook et al., *Molecular Cloning: A laboratory manual* (Cold Spring Harbor Laboratory Press 1989); Ausubel et al., *Current Protocols in Molecular Biology* (Green Publ., NY 1989), each of which is incorporated herein by reference).

A particular nucleotide sequence can be designed based, for example, on a comparison of the nucleic acid molecules encoding any one of the BAG family proteins, as shown in Figures 1-9 and Figures 15-17, with another in the family. Such a comparison allows, for example, the

preparation of a nucleotide sequence that will hybridize to a conserved region present in both nucleic acid molecules, thus providing a means to identify homologous nucleic acid molecules present in other cell types or other organisms. In addition, such a comparison allows the preparation of a nucleotide sequence that will hybridize to a unique region of any of the BAG family nucleotide sequences, such as those corresponding to the BAG domain, thus allowing identification of other proteins sharing this motif. In this regard, it is recognized that, while the human BAG-3 proteins shown as Figures 3 and 20, and human BAG-5 proteins shown as Figures 5 and 24, are only partial sequences, a variant human BAG-3 or BAG-5 produced, for example, by alternative splicing can exist and can be identified using an appropriately designed nucleotide sequence of the invention as a probe. Such useful probes readily can be identified by inspection of the sequences shown in the disclosed Figures by a comparison of the encoding nucleotide sequences.

If desired, a nucleotide sequence of the invention can incorporate a detectable moiety such as a radiolabel, a fluorochrome, a ferromagnetic substance, a luminescent tag or a detectable binding agent such as biotin. These and other detectable moieties and methods of incorporating such moieties into a nucleotide sequence are well known in the art and are commercially available. A population of labelled nucleotide sequences can be prepared, for example, by nick translation of a nucleic acid molecule of the invention (Sambrook et al., *supra*, 1989; Ausubel et al., *supra*, 1989).

One skilled in the art would know that a method involving hybridization of a nucleotide sequence of the invention can require that hybridization be performed under relatively stringent conditions such that nonspecific background hybridization is minimized. Such hybridization

conditions can be determined empirically or can be estimated based, for example, on the relative GC content of a sequence and the number of mismatches, if known, between the probe and the target sequence (see, for example, Sambrook et al., *supra*, 1989).

The invention further provides antibodies specific for human BAG family protein. As used herein, the term "antibody" includes polyclonal and monoclonal antibodies, as well as polypeptide fragments of antibodies that retain a specific binding activity for human BAG-1 of at least about 1×10^5 M^{-1}. One skilled in the art would know that anti-BAG-1 antibody fragments such as Fab, $F(ab')_2$ and Fv fragments can retain specific binding activity for human BAG-1 (beginning at residue 116 of SEQ ID NO:2) and, thus, are included within the definition of an antibody. In addition, the term "antibody" as used herein includes naturally occurring antibodies as well as non-naturally occurring antibodies and fragments that retain binding activity such as chimeric antibodies or humanized antibodies. Such non-naturally occurring antibodies can be constructed using solid phase peptide synthesis, can be produced recombinantly or can be obtained, for example, by screening combinatorial libraries consisting of variable heavy chains and variable light chains as described by Huse et al., *Science* **246**:1275-1281 (1989), which is incorporated herein by reference.

One skilled in the art would know that purified BAG family protein, which can be prepared from natural sources or synthesized chemically or produced recombinantly, or portions of a BAG family protein, including a portion of human BAG family protein such as a synthetic peptide as described above, can be used as an immunogen. Such peptides useful for raising an antibody include, for example, peptide portions of the N-terminal 85 amino acids or the BAG domain of any of the human BAG

proteins (see Figure 1B). A particularly advantageous use of such a protein is for the immunostaining, wherein the methods provides a process to contrast the immunostaining of BAG-family proteins in carcinoma cells with adjacent non-neoplastic prostatic epithelial and basal cells which are generally present in the same tissue sections. These results would be correlated with a Gleason grade to determine whether any of the BAG-family proteins tend to be expressed at higher or lower levels in histologically advanced tumors. From this process a determination can be made as to degree at which the disease is progressing in a given patient, i.e., a prognosis can be made.

Non-immunogenic fragments or synthetic peptides of BAG proteins can be made immunogenic by coupling the hapten to a carrier molecule such bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH), as described in Example IV, below. In addition, various other carrier molecules and methods for coupling a hapten to a carrier molecule are well known in the art and described, for example, by Harlow and Lane, *Antibodies: A laboratory manual* (Cold Spring Harbor Laboratory Press, 1988), which is incorporated herein by reference.

EXAMPLES

The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

BNSDOCID <WO 0014106A1 iA>

EXAMPLE I

Isolation and Characterization of BAG-family cDNA Sequences

This example describes methods for isolating and characterizing of BAG-family cDNA sequences from human, nematode and yeast.

A. Cloning of human BAG cDNA sequences

Yeast two-hybrid library screening of a human Jurkat cell cDNA library was performed as described by Takayama et al., EMBO J., 16:4887-96 (1997); Matsuzawa et al., EMBO J., 17:2736-2747 (1998), which are incorporated herein by reference) using EGY48 strain yeast transformed with pGilda-Hsc70/ATPase (67-377 amino acids) and the *lacZ* reporter plasmid pSH18-34. Of the resulting ~5 x 10^6 transformants, 112 Leu$^-$ colonies were obtained after 1 week incubation at 30°C. Assay of β-galactosidase (β-gal) activity of these colonies resulted in 96 clones. Mating tests were then performed using RFY206 yeast strain transformed with pGilda, pGilda mBAG-1 (1-219), or pGilda Hsc70/ATPase. Of these, 66 displayed specific interactions with Hsc70/ATPase. The pJG4-5 cDNAs were recovered using KC8 *E. coli* strain which is auxotrophic for tryptophan (Trp). DNA sequencing revealed 3 partially overlapping human BAG-1, 4 identical and one overlapping cDNAs encoding BAG-2, and 2 partially overlapping BAG-3 clones.

Using the above described yeast two-hybrid screen with the ATPase domain of Hsc70 as "bait", several human cDNAs were cloned which encode portions of BAG-1 or of two other BAG-1-like proteins which are termed BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6). The longest of the cDNAs for BAG-2 (SEQ ID NO:3) and BAG-3 (SEQ ID NO:5) contained open reading frames (ORFs) of 207 and 162 amino acids, respectively, followed by stop codons. All BAG-1 (SEQ ID

BNSDOCID <WO _0014106A1 IA>

NO:1), BAG-2 (SEQ ID NO:3) and BAG-3 (SEQ ID NO:5) cDNAs obtained by two-hybrid library screening with Hsc70/ATPase contained a conserved domain of about 40-50 amino acids which are termed the "BAG" domain and are shown in Figure 10. These results demonstrate that a family of BAG-1-related proteins all contain a conserved ~45 amino acid region near their C-terminus that binds Hsc70/Hsp70.

B. Identification of additional BAG-family proteins

A search of the translated Genbank database using the bBLAST and FASTA search programs also identified human ESTs that provided sequences for further investigation of BAG-family proteins. The putative BAG-4 (SEQ ID NO:8) and BAG-5 (SEQ ID NO:10) proteins contain BAG-domains that share the greatest sequence similarity with the BAG-domain of BAG-3 (SEQ ID NO:6). These were designated BAG-4 (Accession number AA693697, N74588) and BAG-5 (Accession number AA456862, N34101). BAG-4 has 62% identity and ~81% similarity to BAG-3, and BAG-5 has 51% identity and ~75% similarity to BAG-3.

Additional BAG-family orthologues or homologues were also identified using computer-based searches and resulted in BAG-family homologue in the nematode *C. elegans* and the fission yeast *S. pombe*. The *C. elegans* genome encodes two apparent BAG-family proteins, which are most similar in their overall sequences to the human BAG-1 (Afo39713, gi:2773211) (SEQ ID NO:12) and BAG-2 (SEQ ID NO:14) (Afo68719, gi:3168927). The *S. pombe* contains two BAG-family proteins that share the greatest overall sequence similarity with human BAG-1 (Alo23S54,gi/3133105 and Alo23634, gi/3150250). The human and *C. elegans* BAG-1 proteins as well as *S. pombe* BAG-1A all have ubiquitin-like domains near their N-termini (see Figure 10A) of unknown function.

The overall predicted amino acid sequences of the *C. elegans* BAG-1 (SEQ ID NO:12) and *S. pombe* BAG-1A (SEQ ID NO:16) proteins are ~18% identical (~61% similar) and ~17% identical (~64% similar), respectively, to human BAG-1, implying origin from a common ancestral gene. The *C. elegans* BAG-1 protein (SEQ ID NO:12), however, contains a 5 to 7 amino acid insert in its BAG-domain as compared to the human, murine, and yeast BAG-1 homologues (see Figure 10B), and is more similar to BAG-2 (SEQ ID NO:4) in regard to its BAG-domain. *C. elegans* and human BAG-2 also may be derived from a common ancestor as the C-terminal 225 amino acid region which encompasses both the BAG domain and upstream region of both *C. elegans* and human BAG-2 share ~34% amino acid sequence identity and ~70% similarity. The human BAG-2 protein (SEQ ID NO:4), however, contains a 9 amino acid insert in its BAG-domain compared to it *C.elegans* counterpart (see Figure 10B). Evolutionary-tree prediction algorithms suggest that human and *C. elegans* BAG-2 represent a distinct branch of the BAG-family that is more evolutionarily distant from the other BAG-family proteins. None of the predicted BAG-family proteins contain recognizable regions analogous to those found in other Hsc70 regulatory proteins, such as the J-domains and G/F-domains of DnaJ family proteins and the Tetratricopeptide Repeat (TR) domains of Hip/Hop family proteins.

C. Yeast two-hybrid assay of BAG binding to Hsc70/ATPase

The longest of the cDNAs obtained for the BAG-2 and BAG-3 proteins were expressed with N-terminal transactivation (TA) domains in yeast and tested by yeast two-hybrid assay for interactions with fusion proteins consisting of Hsp70/ATPase or a variety of unrelated proteins (Fas, Siah, Fadd) containing N-terminal LexA DNA-binding domains. TA-BAG-2 and TA-BAG-3 demonstrated

positive interactions with LexA-Hsc70/ATPase, resulting in transactivation of a *lacZ* reporter gene that was under the control of LexA operators (Figure 11A). No interactions with LexA-Fas (cytosolic domain), LexA-Siah, LexA-Fadd, or LexA were detected (see Figure 11A) demonstrating that the BAG-2 and BAG-3 proteins interact specifically with Hsc70/ATPase. Specific two-hybrid interactions between Hsc70/ATPase and either BAG-2 or BAG-3 were also observed when BAG-2 and BAG-3 were expressed as LexA DNA-binding domain fusion proteins and Hsc70/ATPase was fused with a TA domain (see Figure 11A; right panel). These results demonstrate that similarly to BAG-1, BAG-2 and BAG-3 specifically interact with Hsc70/ATPase.

In order to determine whether the BAG proteins are capable of forming heterodimers, coexpression of BAG-2 and BAG-3 in the yeast two-hybrid assay was also performed. Coexpression of BAG-2 and BAG-3 failed to show interaction with BAG-1 or a deletion mutant of BAG-1 (ΔC) which is missing part of its C-terminal domain required for Hsp70/Hsc70 binding suggest that these proteins do not form heterdimers.

D. Isolation and characterization of the complete open reading frame sequences of BAG-2 and BAG-3

In order to deduce the complete ORFs of BAG-2 and BAG-3, a λ-phage cDNA library was screened as follows, using hybridization probes derived from the two-hybrid screening. A human jurkat T-cell λ-ZapII library cDNA library (Stratagene) was screened by hybridization using ^{32}P-labeled purified insert DNA from the longest of the human BAG-2 (clone #11) and human BAG-3 (clone #28) cDNA clones. From about one million clones screened, 38 BAG-2 and 23 BAG-3 clones were identified, cloned, and their cDNA inserts recovered as pSKII plasmids using a helper phage method (Stratagene). DNA sequencing of λ-phage derived

human BAG-2 cDNA clones revealed an ORF encoding a predicted 211 amino acid protein, preceded by an in-frame stop codon. The longest human BAG-3 λ-phage cDNA clone contains a continuous ORF of 682 amino acids followed by a stop codon, but without an identifiable start codon (see Figure 10A).

Although BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) all contain a homologous BAG domain near their C-terminus, the N-terminal regions of these proteins are dissimilar. Using a combination of search tools (Prosite Search: PP search, using the Prosite pattern database, BCM Search Launcher, Baylor College of Medicine, and Blocks Search), it was determined that the BAG-2 N-terminal region contains potential kinase phosphorylation sites but otherwise shares no apparent similarity with other proteins or known functional domains.

In contrast, the predicted N-terminal region BAG-3 contains a WW domain as shown in Figure 10A. WW domains have been identified in a wide variety of signaling proteins, including a Yes kinase adaptor protein (YAP), the Na^+-channel regulator Nedd4, formin-binding proteins, dystrophin, and the peptidyl prolyl cis-trans-isomerase Pin-1. These roughly 40 amino acid domains mediate protein interactions and bind the preferred peptide ligand sequence xPPxY (Sudol., TIBS, 21: 161-163, 1996, which is incorporated herein by reference).

EXAMPLE II

In vitro Association of BAG proteins and Hsc70/ATPase

This example demonstrates that BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) bind Hsc70/ATPase in various *in vitro* assays.

A. Solution binding assay of BAG-2 and BAG-3 to Hsc70/ATPase

Association of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) with Hsc70/ATPase was determine by an *in vitro* protein binding assay where Hsc70/ATPase or BAG-family proteins were expressed in bacteria as Glutathione S-Transferase (GST) fusion proteins. Purified cDNA sequences encoding residues 5 to 211 of human BAG-2 (clone #11) and the C-terminal 135 amino acids of human BAG-3 (clone #28) (see Figure 10A) were subcloned into the EcoRI/Xho I sites of pGEX4T-1 prokaryotic expression plasmid (Pharmacia; Piscataway, NJ). These plasmids as well as pGEX4T-1-BAG-1, pGEX-4T-1-BAG-1 (ΔC), and pGEX-4T-1-XL which have been described previously (Takayama et al.,*supra* (1997); Xie et al., Biochemistry, 37:6410-6418, (1998), which are incorporated herein by reference), were expressed in XL-1 blue strain *E. Coli* (Stratagene, Inc., La Jolla, CA). Briefly, a single colony was inoculated into 1L of LB media containing 50 μg/ml ampicillin and grown at 37°C overnight. The culture was then diluted by half with fresh LB/ampicillin and cooled to room temperature for 1 hr, before inducing with 0.4mM IPTG for 6 h at 25°C.

Cells were recovered and incubated with 0.5 mg/ml lysozyme in 50 mM Tris (pH 8.0), 150 mM NaCl, 1% Tween-20, 0.1% 2-mercaptoethanol, 5 mM EDTA, 1 mM PMSF and a mixture

BNSDOCID <WO 0014106A1 IA>

of other protease inhibitors obtained from Boehringer Mannheim (1697498) at room temperature for 0.5 h, followed by sonication. Cellular debris were pelleted by centrifugation at 27,500g for 10 min and the resulting supernatants were incubated with 30 ml of glutathionine-Sepharose (Pharmacia) at 4°C overnight. The resin was then washed with 20 mM Tris (pH 8.0), 150 mM NaCl, 0.1% Tween-20, and 0.1% 2-mercaptoethanol until the OD 280nm reached <0.01. For removal of GST, the resin with immobilized GST-fusion protein was incubated with 10U of thrombin (Boehringer, Inc.) at 4°C in 20 mM Tris (pH 8.0), 150 mM NaCl, 0.1% Tween-20, 0.1% 2-Mercaptoethanol, and 2.5 mM CaCl2 overnight. Released proteins were then purified on Mono Q (HR10/10, Pharmacia) by FPLC using a linear gradient of 0.5M NaCl at pH 8.0 and dialyzed into chaperone assay buffer.

The ability of BAG-2 (SEQ ID NO:4) or BAG-3 (SEQ ID NO:6) to bind Hsc70/ATPase in solution was then examined. GST control or GST-BAG proteins were immobilized on glutathione-Sepharose and tested for binding to 35S-labeled *in vitro* translated (IVT) proteins. Immunoprecipitation and *in vitro* GST-protein binding assays were performed as described by Takayama et al., *supra* (1997), using pCI-Neo flag or pcDNA3-HA into which human Bag-2 (clone #11) or human BAG-3 (clone #28) had been subcloned for *in vitro* translation of 35S-L-methionine labeled proteins or expression in 293T cells. As shown in Figure 11B, ^{35}S-Hsc70/ATPase bound *in vitro* to GST-BAG-1, GST-BAG-2, and GST-BAG-3 but not to GST-BAG-1(ΔC) or several other control proteins. BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) also exhibited little or no binding to themselves or to each other, demonstrating that these proteins do not strongly homo- or hetero-dimerize or oligomerize. It should be noted, however, that BAG-2 (SEQ

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ID NO:4) displayed weak interactions with itself in binding assays and produced a positive result in yeast two-hybrid experiments, demonstrating that it can have the ability to self-associate.

B. Binding of BAG proteins to Hsc70 *in vivo*

The ability of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins to interact in cells with Hsc70 was tested by expressing these proteins with N-terminal Flag epitope tags in 293T human epithelial cells using co-immunoprecipitation assays as described previously (Takayama et al., *supra* (1997)). cDNAs encoding the λ-phage cloned regions of BAG-2 and BAG-3 were subcloned in-frame into pcDNA3-Flag. Anti-Flag immune complexes prepared from 293T cells after transfection with plasmids encoding Flag-BAG-1, Flag-BAG-2, or Flag-BAG-3 were analyzed by SDS-PAGE/immunoblot assay. As shown in Figure 10C, antiserum specific to Hsc70 detected the presence of BAG proteins associated with Hsc70, whereas control immune-complexes prepared with IgG1 as well as anti-Flag immune complexes prepared from cells transfected with Flag-tagged control proteins, Daxx and Apaf-1, did not contain Hsc70 associated protein. These results further demonstrate that BAG-family proteins specifically bind to Hsc70.

C. BIAcore assay of BAG protein binding to the ATPase domain of Hsc70

BAG-1 (beginning at residue 116 of SEQ ID NO:2) is known to bind tightly to the ATPase domain of Hsc70 (Stuart et al., J. Biol. Chem., In Press (1998)). BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins were therefore, examined for their ability to bind to Hsc70/ATPase. The affinity and binding kinetics of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) to Hsc70/ATPase was also compared to that of BAG-1 (beginning at residue 116 of

BNSDOCID <WO 0014106A1 IA>

SEQ ID NO:2) for Hsc70/ATPase, using a surface plasmon resonance technique (BIAcore) which has been described previously (Stuart et al., *supra*, (1998) which is incorporated herein by reference).

BAG-family proteins were produced in bacteria and purified to near homogeneity as shown in Figure 12A and described above in Example I. The purified BAG-1 (beginning at residue 116 of SEQ ID NO:2), -2 (SEQ ID NO:4), and -3 (SEQ ID NO:6) proteins were then immobilized on biosensor chips and tested for their interactions with Hsc70 in the soluble phase. Kinetic measurements were performed using a BIAcore-II instrument with CM5 sensor chip and Amine Coupling Kit (Pharmacia Biosensor AB, Sweden). Briefly, for immobilization of proteins, the sensor chip was equilibrated with HK buffer (10 mM Hepes (pH 7.4), 150 mM KCL) at 5μl/min, then activated by injecting 17 μl of 0.2M N-ethyl-N'-(3-diethylaminopropyl)-carbodiimide and 0.05M N-hydroxysuccinimide (NHS/EDC) followed by 35 μl of the protein of interest, in 10 mM acetate, pH 3.5-4.5. Excess NHS-ester on the surface was deactivated with 17 μl 1M ethanolamine-HCL (pH8.5). After immobilization, 5μl of regeneration buffer (50 mM phosphate (pH 6.8) and 4M GuHCl) was injected. For binding assays, Hsp70 (Sigma, H8778) was dissolved in HK buffer, and injected at 10 μl/min across the prepared surface at various concentrations. The surface was regenerated after each injection with 5 μl of regeneration buffer. The rate constants K_{ass} and K_{diss} were generated with BIAevaluation softward 3.01 (Pharmacia Biosensor AB). Addition of Hsc70 to chips containing BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4) or BAG-3 (SEQ ID NO:6) resulted in concentration-dependent binding, as reflected by an increase in the Response Units (RU) measured at the chip surface (shown in Figure 3B). In contrast, Hsc70 failed to display interactions in BIAcore assays with a variety of control proteins as well as a mutant of BAG-1

BNSDOCID <WO 0014106A1 A>

lacking a C-terminal portion of the BAG domain which is required for Hsc70-binding (Figure 3B). Furthermore, flowing of various control proteins such as GST, BSA and Bcl-XL over the BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) chips resulted in negligible interaction. These results further demonstrate the specificity with which BAG-family proteins interact with and bind to Hsc70.

The rates of Hsc70 binding to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) proteins were similar, following pseudo first-order kinetics with estimated association rate constants (K_a) of 2.1, 2.1 and 2.4 x 10^5 M^{-1} sec^{-1}, respectively. After allowing binding of Hsc70 to immobilized BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) to reach plateau levels, the chaperone was removed from the flow solution and the dissociation rate was monitored. BAG-1 (beginning at residue 116 at SEQ ID NO:2) and BAG-2 (SEQ ID NO:4) exhibited similar dissociation rates, with relatively slow loss of Hsc70 from the chip surface, resulting in estimated dissociation rate constants (K_d) of 3.0 and 5.0 x 10^{-4} sec^{-1}, respectively (see Figure 3B). In contrast, Hsc70 dissociated more rapidly from biosensor chips containing BAG-3 (see Figure 3B), yielding an estimated K_d of 1.7 x 10^{-3} sec^{-1}. From the kinetic data, the apparent affinities (K_D = K_d/K_a) were calculated for binding of Hsc70 to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) and were estimated to equal about K_D= 1.4nM, K_D=2.4nM, and K_D=7.4nM, respectively. These results demonstrate that the interactions of BAG-family proteins with Hsc70 occur with apparent affinities sufficient for physiological relevance.

BNSDOCID <WO 0014106A1 IA>

EXAMPLE III

BAG-family proteins inhibit Hsp70/Hsc70-dependent protein folding

This example demonstrates that BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins inhibit Hsp70/Hsc70-dependent refolding of denatured proteins similarly to a BAG-1 (beginning at residue 116 of SEQ ID NO:2) protein.

The effects of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) protein on Hsp70/Hsc70-dependent protein refolding was determined using *in vitro* protein refolding assays similar to those described previously by Takayama et al., *supra*, 1998; Terada et al., J Cell Biol., 139:1089-1095, 1997, which are incorporated herein by reference. Briefly, luciferase (20μM) was denatured in 25 mM Hepes-KOH, pH 7.2, 50 mM potassium acetate, 5 mM DTT, 6M guanidine hydrochloride at ~25°C for 1 h. Denatured luciferase was diluted 1:40 into 25 mM Hepes-KOH, pH 7.2, 50 mM potassium acetate, 5 mM DTT. Hsc70 (1.8 μM), DnaJ (StressGen, Inc.) (0.9μM), and various purified recombinant proteins as indicated were added to refolding buffer (30 mM Hepes-KOH, pH 7.6, 120 mM potassium acetate, 3mM magnesium acetate, 2 mM DTT, 2.5 mM ATP) with 0.2 volume of diluted denatured luciferase to a final concentration of 0.1 μM. Luciferase activity was measured after 1.5 hr incubation at 35°C.

The combination of Hsc70 and DnaJ resulted in ATP-dependent refolding of chemically denatured firefly luciferase, with function of over half the denatured enzyme restored in a 90 minute reaction, as monitored by a chemiluminescence assay. In contrast, neither Hsc70 nor DnaJ alone were able to induce substantial refolding of denatured luciferase. Furthermore, little spontaneous

restoration of luciferase activity was observed with control proteins, BSA, GST or Bcl-XL (see Figure 4A).

Addition of recombinant purified BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) to the above assays in amounts equimolar to Hsc70 (1.8 μM) resulted in striking inhibition of luciferase refolding. BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) displayed somewhat greater inhibitory activity than BAG-1 (beginning at residue 116 of SEQ ID NO:2) as shown in Figure 4A. In contrast, the BAG-1 (ΔC) protein, which fails to bind Hsc70 as well as several other control proteins, had no effect on luciferase refolding.

In an additional refolding assay, described previously by Minami et al., J Biol. Chem. 271:19617-24, 1996), purified Hsc70 and human DnaJ homolog Hdj-1 (Hsp 40) were used with additional cofactors provided in reticulocyte lysates (5% v:v) to produce a system capable of refolding denatured luciferase. Briefly, additional cofactors included, recombinant Luciferase (Promega: QuantiLum TM), that had been heat denatured at 42°C for 10 min, 1.8 μM Hsc70 (Sigma; purified from bovine brain), 0.9 μM Hsp40, and various recombinant purified proteins. Luciferase activity was measured (Promega luciferase assay kit) using a luminometer (EG&G Berthold, MicroLumat luminometer, Model #LB96P). All results were normalized relative to non-denatured luciferase that had been subjected to the same conditions. Control reactions lacking ATP, Hsc70, or Hsp40 resulted in negligible luciferase refolding.

Various amounts of purified BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6), relative to amounts of Hsc70 were used in the above-described protein refolding assay. Addition of BAG-family proteins resulted in a concentration-dependent

BNSDOCID <WO 0014106A1 IA>

inhibition of Hsc70 chaperone activity. Furthermore, the BAG-2 (SEQ ID NO:4)and BAG-3 (SEQ ID NO:6) inhibition of Hsc70 chaperone activity was demonstrated to be as potent as that observed for BAG-1 (beginning at residue 116 of SEQ ID NO:2). In contrast, the BAG-1 (ΔC) mutant as well as other control proteins did not suppress Hsc70-mediated refolding of denatured luciferase. These results indicate that BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) can inhibit Hsc70/Hsp70 dependent protein refolding activity to the same extent as BAG-1 (beginning at residue 116 of SEQ ID NO:2).

B. BAG competes with Hip for binding to Hsc70.

It is known that BAG-1 competes with Hip for binding to Hsc70, with these proteins exerting opposite effects on Hsc70-mediated protein refolding (Hohfeld, J., and Jentsch, S., *Embo J.*, 16:6209-6216, 1997, which is incorporated herein by reference). In order to determine whether BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) also compete with Hip for binding to Hsc70, refolding assays were performed as described above in the presence of Hip protein.

Hip was purified as His_6-protein. The fusion protein was induced from pET28-Hip (V. Prapapanich et al., *Mol Cell Biol.*, 18:944-952, 1998, which is incorporated herein by reference) with 0.1 mM IPTG at 25°C for 6h in BL21 cells. Cells from 1L of culture were resuspended into 50 ml of 50 mM Phosphate buffer (pH 6.8), 150 mM NaCl, and 1% (v/v) Tween-20 and then incubated with 0.5 mg/ml lysozyme at 25°C for 0.5h, followed by sonication. After centrifugation at 27,500g for 10 min, the resulting supernatant was mixed with 15 ml nickel resin (Qiagen, Inc.) at 4°C for 3 h with 25 mM imidazol. The resin was then washed with 50 mM phosphate buffer (pH 6.8), 25 mM imidazol, 150 mM NaCl and 0.1% Tween-20 until the OD280nm

reached a value of <0.01. His_6-Hip protein was eluted with 250 mM imidazol in washing buffer (Qiagene, Inc.) and purified on Mono Q (HR10/10 Pharmacia) by FPLC using a linear gradient of 0.5M NaCl at pH 8.0, followed by dialysis in chaperone assay buffer.

In the refolding assay reactions, addition of purified Hip at equimolar concentrations relative to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) (1.8 μM) completely negated the inhibitory effects of the BAG-family proteins on refolding of denatured luciferase (see Figure 4C). These results demonstrate that the suppression of Hsc70 chaperone activity by BAG-family proteins is reversible, and that Hip antagonizes the effects of not only BAG-1 (beginning at residue 116 of SEQ ID NO:2), but also of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6).

In summary, these results demonstrate that BAG-family proteins all contain a conserved BAG domain near their C-terminus that binds Hsc70/Hsp70, and that human BAG-family proteins can bind with high affinity to the ATPase domain of Hsc70 and inhibit its chaperone activity through a Hip-repressable mechanism.

EXAMPLE IV

EXPANDED NUCLEIC ACID AND AMINO ACID SEQUENCES FOR HUMAN BAG-3, BAG-4 AND BAG-5

Following the procedures disclosed herein, the nucleic acid and amino acids sequences to human BAG-3, BAG-4 and BAG-5 were further expanded. The expanded sequences for BAG-3, BAG-4 and BAG-5 are shown in Figures 15, 16 and 17, respectively, with their respective sequence identification numbers, "SEQ ID NO"s.

BNSDOCID <WO 0014106A1 IA>

We claim:

1. A compound of the formula,

$$R^N\text{-}R^1X^1R^2X^2R^3X^3R^4X^4R^5X^5R^6X^6R^7X^7X^8R^9X^9R^{10}X^{10}R^{11}X^{11}\text{-}R^C$$

wherein,

R^N is a group of about 1 to 552 independently selected amino acids;

R^1 is a group of 3 independently selected amino acids;

X^1 is an amino acid with a charged or uncharged R group;

R^2 is a group of 7 independently selected amino acids;

X^2 is an amino acid with a charged R group;

R^3 is a group of 5 independently selected amino acids;

X^3 is an amino acid with an apolar R group;

R^4 is a group of 3 independently selected amino acids;

X^4 is an amino acid with charged R group;

R^5 is a single independently selected amino acid;

X^5 is an amino acid with apolar or uncharged R group;

R^6 is a group of 15 independently selected amino acids;

X^6 is an amino acid with a charged or uncharged R group;

R^7 is a group of 2 independently selected amino acids;

X^7 is an amino acid with a charged R group;

X^8 is an amino acid with a charged R group;

R^9 is a group of 2 independently selected amino acids;

X^9 is an amino acid with an apolar R group;

BNSDOCID <WO 0014106A1 IA>

R^{10} is a group of 3 independently selected amino acids;

X^{10} is an amino acid with an uncharged R group;

R^{11} is a group of 2 independently selected amino acids;

X^{11} is an amino acid with an apolar R group; and

R^{C} is a group of about 1 to 100 independently selected amino acids.

2. A substantially purified nucleic acid molecule having a nucleotide sequence corresponding to or complementary to at least 20 nucleotides from a nucleotide sequence selected from the group consisting of (SEQ ID NO:1), (SEQ ID NO:3), (SEQ ID NO:5), (SEQ ID NO:7), (SEQ ID NO:9), (SEQ ID NO:19), (SEQ ID NO:21) and (SEQ ID NO:23).

3. The nucleic acid of claim 2 having a nucleotide sequence corresponding to or complementary to a nucleotide sequence that encodes a functionally active BAG family protein selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24).

4. The nucleic acid of claim 3 selected from the group consisting of (SEQ ID NO:1), (SEQ ID NO:3), (SEQ ID NO:5), (SEQ ID NO:7), (SEQ ID NO:9), (SEQ ID NO:19), (SEQ ID NO:21) and (SEQ ID NO:23).

5. The nucleic acid of claim 3 complementary to a nucleotide sequence that encodes a functionally active BAG protein selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24).

6. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:3).

BNSDOCID <WO 0014106A1 IA>

7. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:5).

8. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:7).

9. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:9).

10. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:19).

11. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:21).

12. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:23).

13. A substantially purified BAG family protein encoded by the nucleic acid molecule of claim 1.

14. A substantially purified BAG family protein comprising of the amino acid sequence selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24) or a fragment, a derivative or a mimetic thereof.

15. A substantially purified protein corresponding to the amino acid sequence of 157 to 204 of (SEQ ID NO:2).

16. A substantially purified protein corresponding to the amino acid sequence of 272 to 319 of (SEQ ID NO:2).

17. A substantially purified protein corresponding to the amino acid sequence of 164 to 211 of (SEQ ID NO:4).

18. A substantially purified protein corresponding to the amino acid sequence of 418 to 510 of (SEQ ID NO:20).

19. A substantially purified protein corresponding to the amino acid sequence of 378 to 457 of (SEQ ID NO:22).

20. A substantially purified protein corresponding to the amino acid sequence of 6 to 97 of (SEQ ID NO:24).

21. A substantially purified protein corresponding to the amino acid sequence of 180 to 257 of (SEQ ID NO:24).

22. A substantially purified protein corresponding to the amino acid sequence of 272 to 349 of (SEQ ID NO:24).

23. A substantially purified protein corresponding to the amino acid sequence of 362 to 444 of (SEQ ID NO:24).

24. A pharmaceutical composition comprising a nucleic acid molecule of claim 1 useful for modulating tumor cell proliferation, cell migration and metastasis, and steroid hormone receptor function.

25. A method of modulating tumor cell proliferation, cell migration and metastasis, and steroid hormone receptor function by administering a nucleic acid molecule of claim 1.

26. A pharmaceutical composition comprising a substantially purified BAG family protein comprising of the amino acid sequence selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24), or a fragment, a derivative or a mimetic thereof, useful for modulating tumor cell proliferation, cell migration and metastasis, and steroid hormone receptor function.

27. A method of modulating tumor cell proliferation by administering a pharmaceutical composition of claim 26.

28. A method of modulating cell migration and metastasis by administering a pharmaceutical composition of claim 26.

29. A method of modulating steroid hormone receptor function by administering a pharmaceutical composition of claim 26.

30. A substantially purified antibody that specifically binds to a BAG family protein of claim 14.

31. The antibody of claim 30, wherein said antibody is a monoclonal antibody.

32. A method for detecting the presence of a BAG family protein in a sample, comprising the steps of:

a. obtaining the sample;

b. adding to said an antibody of claim 11 under suitable conditions for the binding of said antibody with the BAG family protein; and

c. detecting said bound BAG family protein.

33. A method for detecting the presence of a first nucleic acid molecule that encodes a BAG family protein in a sample, comprising the steps of:

a. obtaining the sample;

b. adding to said sample a second nucleic acid molecule capable of hybridizing with said first nucleic acid molecule under suitable conditions for the binding of said second nucleic acid molecule with said first nucleic acid molecule; and

c. detecting said hybridized first and second nucleic acid molecules.

34. A method of determining the risk of metastatic spread of cancer or prognosis of cancer patients by determining the level of expression of a BAG-family protein.

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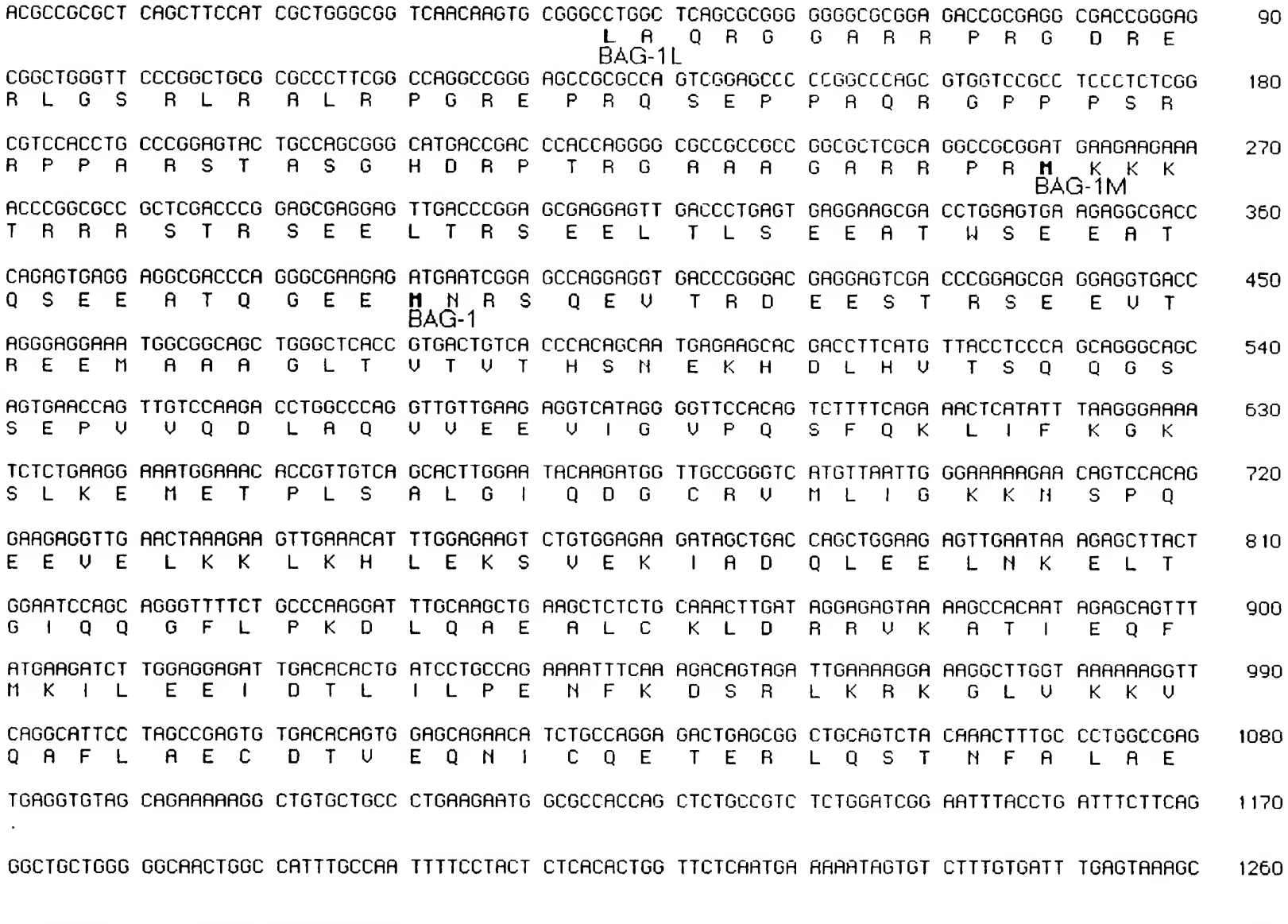

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CGTCCACCTG CCCGGAGTAC TGCCAGCGGG CATGACCGAC CCACCAGGGG CGCCGCCGCC GGCGCTCGCA GGCCGCGGAT GAAGAAGAAA 270

ACCCGGCGCC GCTCGACCCG GAGCGAGGAG TTGACCCGGA GCGAGGAGTT GACCCTGAGT GAGGAAGCGA CCTGGAGTGA AGAGGCGACC 360

CAGAGTGAGG AGGCGACCCA GGGCGAAGAG ATGAATCGGA GCCAGGAGGT GACCCGGGAC GAGGAGTCGA CCCGGAGCGA GGAGGTGACC 450

AGGGAGGAAA TGGCGGCAGC TGGGCTCACC GTGACTGTCA CCCACAGCAA TGAGAAGCAC GACCTTCATG TTACCTCCCA GCAGGGCAGC 540

AGTGAACCAG TTGTCCAAGA CCTGGCCCAG GTTGTTGAAG AGGTCATAGG GGTTCCACAG TCTTTTCAGA AACTCATATT TAAGGGAAAA 630

TCTCTGAAGG AAATGGAAAC ACCGTTGTCA GCACTTGGAA TACAAGATGG TTGCCGGGTC ATGTTAATTG GGAAAAAGAA CAGTCCACAG 720

GAAGAGGTTG AACTAAAGAA GTTGAAACAT TTGGAGAAGT CTGTGGAGAA GATAGCTGAC CAGCTGGAAG AGTTGAATAA AGAGCTTACT 810

GGAATCCAGC AGGGTTTTCT GCCCAAGGAT TTGCAAGCTG AAGCTCTCTG CAAACTTGAT AGGAGAGTAA AAGCCACAAT AGAGCAGTTT 900

ATGAAGATCT TGGAGGAGAT TGACACACTG ATCCTGCCAG AAAATTTCAA AGACAGTAGA TTGAAAAGGA AAGGCTTGGT AAAAAAGGTT 990

CAGGCATTCC TAGCCGAGTG TGACACAGTG GAGCAGAACA TCTGCCAGGA GACTGAGCGG CTGCAGTCTA CAAACTTTGC CCTGGCCGAG 1080

TGAGGTGTAG CAGAAAAAGG CTGTGCTGCC CTGAAGAATG GCGCCACCAG CTCTGCCGTC TCTGGATCGG AATTTACCTG ATTTCTTCAG 1170

GGCTGCTGGG GGCAACTGGC CATTTGCCAA TTTTCCTACT CTCACACTGG TTCTCAATGA AAAATAGTGT CTTTGTGATT TGAGTAAAGC 1260

TCCTATTCTG TTTTTCACAA AAAAAAAAAA A 1291

FIG. 1

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FIG. 2A

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                                                                                                                    90
GCAGCCGCGG TGTCGCGAAG TCCTCCCGGG TTGCCCCCGC GGCGTCAGAG GGAGGGCGGG CGCCGCGTTG GTGACGGCGA CCCTGCAGCC
CAAGGAGCGC TCCACTCGCT GCCGCCGGAG GGCCGGTGAC CTCTTGGCTA CCCCGCGTCG GAGGCTTAGA TGGCTCAGGC GAAGATCAAC   180
                                                                                  .  M   A  Q  A   K  I  N

GCTAAAGCCA ACGAGGGGCG CTTCTGCCGC TCCTCCTCCA TGGCTGACCG CTCCAGCCGC CTGCTGGAGA GCCTGGACCA GCTGGAGCTC   270
A  K  A  N   E  G  R   F  C  R   S  S  S  M   A  D  R   S  S  R   L  L  E  S   L  D  Q   L  E  L

AGGGTTGAAG CTTTGAGAGA AGCAGCAACT GCTGTTGAGC AAGAGAAAGA AATCCTTCTG GAAATGATCC ACAGTATCCA AAATAGCCAG   360
R  V  E  A   L  R  E   A  A  T   A  V  E  Q   E  K  E   I  L  L   E  M  I  H   S  I  Q   N  S  Q

GACATGAGGC AGATCAGTGA CGGAGAAAGA GAAGAATTAA ATCTGACTGC AAACCGTTTG ATGGGAAGAA CTCTCACCGT TGAAGTGTCA   450
D  M  R  Q   I  S  D   G  E  R   E  E  L  N   L  T  A   N  R  L   M  G  R  T   L  T  V   E  V  S

GTAGAAACAA TTAGAAACCC CCAGCAGCAA GAATCCCTAA AGCATGCCAC AAGGATTATT GATGAGGTGG TCAATAAGTT TCTGGATGAT   540
V  E  T  I   R  N  P   Q  Q  Q   E  S  L  K   H  A  T   R  I  I   D  E  V  V   N  K  F   L  D  D

TTGGGAAATG CCAAGAGTCA TTTAATGTCG CTCTACAGTG CATGTTCATC TGAGGTGCCA CATGGGCCAG TTGATCAGAA GTTTCAATCC   630
L  G  N  A   K  S  H   L  M  S   L  Y  S  A   C  S  S   E  V  P   H  G  P  V   D  Q  K   F  Q  S

ATAGTAATTG GCTGTGCTCT TGAAGATCAG AAGAAAATTA AGAGAAGATT AGAGACTCTG CTTAGAAATA TTGAAAACTC TGACAAGGCC   720
I  V  I  G   C  A  L   E  D  Q   K  K  I  K   R  R  L   E  T  L   L  R  N  I   E  N  S   D  K  A

ATCAAGCTAT TAGAGCATTC TAAAGGAGCT GGTTCCAAAA CTCTGCAACA AAATGCTGAA AGCAGATTCA ATTAGTCTTC AAACCTAAGA   810
I  K  L  L   E  H  S   K  G  A   G  S  K  T   L  Q  Q   N  A  E   S  R  F  N
```

```
GCATTTACAC AATACACAAG GTGTAAAAAT GATAAAATAC TATTTTAATT GATAACTAGT TCTTTGTTAG GTATAACCAC TTAGTTGACA   900
CTGATAGTTG TTTCAGATGA GGAAAATATT CCATCAAGTA TCTTCAGTTT TGTGAATAAC AAAACTAGCA ATATTTTAAT TATCTATCTA   990
GAGATTTTTT AGATTGAATT CTTGTCTTGT ACTAGGATCT AGCATATTTC ACTATTCTGT GGATGAATAC ATAGTTTGTG GGGAAAACAA  1080
ACGTTCAGCT AGGGGCAAAA AGCATGACTG CTTTTCCTG TCTGGCATGG AATCACGCAG TCACCTTGGG CATTTAGTTT ACTAGAAATT  1170
CTTTACTGG                                                                                           1179
```

FIG. 2B

BNSDOCID <WO 0014106A1 IA>

```
GCGGAGCTCC GCATCCAACC CCGGGCCGCG GCCAACTTCT CTGGACTGGA CCAGAAGTTT CTAGCCGGCC AGTTGCTACC TCCCTTTATC     90
A  E  L  R     I  Q  P     R  A  A     A  N  F  S     G  L  D     Q  K  F     L  A  G  Q     L  L  P     P  F  I

TCCTCCTTCC CCTCTGGCAG CGAGGAGGCT ATTTCCAGAC ACTTCCACCC CTCTCTGGCC ACGTCACCCC CGCCTTTAAT TCATAAAGGT    180
S  S  F  P     S  G  S     E  E  A     I  S  R  H     F  H  P     S  L  A     T  S  P  P     P  L  I     H  K  G

GCCCGGCGCC GGCTTCCCGG ACACGTCGGC GGCGGAGAGG GGCCCACGGC GGCGGCCCGG CCAGAGACTC GGCGCCCGGA GCCAGCGCCC    270
A  R  R  R     L  P  G     H  V  G     G  G  E  G     P  T  A     A  A  R     P  E  T  R     R  P  E     P  A  P

CGCACCCGCG CCCCAGCGGG CAGACCCCAA CCCAGCATGA GCGCCGCCAC CCACTCGCCC ATGATGCAGG TGGCGTCCGG CAACGGTGAC    360
R  T  R  A     P  A  G     R  P  Q     P  S  M  S     A  A  T     H  S  P     M  M  Q  V     A  S  G     N  G  D

CGCGACCCTT TGCCCCCCGG ATGGGAGATC AAGATCGACC CGCAGACCGG CTGGCCCTTC TTCGTGGACC ACAACAGCCG CACCACTACG    450
R  D  P  L     P  P  G     W  E  I     K  I  D  P     Q  T  G     W  P  F     F  V  D  H     N  S  R     T  T  T

TGGAACGACC CGCGCGTGCC CTCTGAGGGC CCCAAGGAGA CTCCATCCTC TGCCAATGGC CCTTCCCGGG AGGGCTCTAG GCTGCCGCCT    540
W  N  D  P     R  V  P     S  E  G     P  K  E  T     P  S  S     A  N  G     P  S  R  E     G  S  R     L  P  P

GCTAGGGAAG GCCACCCTGT GTACCCCAG CTCCGACCAG GCTACATTCC CATTCCTGTG CTCCATGAAG GCGCTGAGAA CCGGCAGGTG    630
A  R  E  G     H  P  V     Y  P  Q     L  R  P  G     Y  I  P     I  P  V     L  H  E  G     A  E  N     R  Q  V

CACCCTTTCC ATGTCTATCC CCAGCCTGGG ATGCAGCGAT TCCGAACTGA GGCGGCAGCA GCGGCTCCTC AGAGGTCCCA GTCACCTCTG    720
H  P  F  H     V  Y  P     Q  P  G     M  Q  R  F     R  T  E     A  A  A     A  A  P  Q     R  S  Q     S  P  L

CGGGGCATGC CAGAAACCAC TCAGCCAGAT AAACAGTGTG GACAGGTGGC AGCGGCGGCG GCAGCCCAGC CCCCAGCCTC CCACGGACCT    810
R  G  M  P     E  T  T     Q  P  D     K  Q  C  G     Q  V  A     A  A  A     A  A  Q  P     P  A  S     H  G  P

GAGCGGTCCC AGTCTCCAGC TGCCTCTGAC TGCTCATCCT CATCCTCCTC GGCCAGCCTG CCTTCCTCCG GCAGGAGCAG CCTGGGCAGT    900
E  R  S  Q     S  P  A     A  S  D     C  S  S  S     S  S  S     A  S  L     P  S  S  G     R  S  S     L  G  S

CACCAGCTCC CGCGGGGGTA CATCTCCATT CCGGTGATAC ACGAGCAGAA CGTTACCCGG CCAGCAGCCC AGCCCTCCTT CCACAAAGCC    990
H  Q  L  P     R  G  Y     I  S  I     P  V  I  H     E  Q  N     V  T  R     P  A  A  Q     P  S  F     H  K  A

CAGAAGACGC ACTACCCAGC GCAGAGGGGT GAGTACCAGA CCCACCAGCC TGTGTACCAC AAGATCCAGG GGGATGACTG GGAGCCCCGG   1080
Q  K  T  H     Y  P  A     Q  R  G     E  Y  Q  T     H  Q  P     V  Y  H     K  I  Q  G     D  D  W     E  P  R

CCCCTGCGGG CGGCATCCCC GTTCAGGTCA TCTGTCCAGG GTGCATCGAG CCGGGAGGGC TCACCAGCCA GGAGCAGCAC GCCACTCCAC   1170
P  L  R  A     A  S  P     F  R  S     S  V  Q  G     A  S  S     R  E  G     S  P  A  R     S  S  T     P  L  H

TCCCCCTCGC CCATCCGTGT GCACACCGTG GTCGACAGGC CTCAGCAGCC CATGACCCAT CGAGAAACTG CACCTGTTTC CCAGCCTGAA   1260
S  P  S  P     I  R  V     H  T  V     V  D  R  P     Q  Q  P     M  T  H     R  E  T  A     P  V  S     Q  P  E

AACAAACCAG AAAGTAAGCC AGGCCCAGTT GGACCAGAAC TCCCTCCTGG ACACATCCCA ATTCAAGTGA TCCGCAAAGA GGTGGATTCT   1350
N  K  P  E     S  K  P     G  P  V     G  P  E  L     P  P  G     H  I  P     I  Q  V  I     R  K  E     V  D  S

AAACCTGTTT CCCAGAAGCC CCCACCTCCC TCTGAGAAGG TAGAGGTGAA AGTTCCCCCT GCTCCAGTTC CTTGTCCTCC TCCCAGCCCT   1440
K  P  V  S     Q  K  P     P  P  P     S  E  K  V     E  V  K     V  P  P     A  P  V  P     C  P  P     P  S  P

GGCCCTTCTG CTGTCCCCTC TTCCCCCAAG AGTGTGGCTA CAGAAGAGAG GGCAGCCCCC AGCACTGCCC CTGCAGAAGC TACACCTCCA   1530
G  P  S  A     V  P  S     S  P  K     S  V  A  T     E  E  R     A  A  P     S  T  A  P     A  E  A     T  P  P

AAACCAGGAG AAGCCGAGGC TCCCCCAAAA CATCCAGGAG TGCTGAAAGT GGAAGCCATC CTGGAGAAGG TGCAGGGGCT GGAGCAGGCT   1620
K  P  G  E     A  E  A     P  P  K     H  P  G  V     L  K  V     E  A  I     L  E  K  V     Q  G  L     E  Q  A

GTAGACAACT TTGAAGGCAA GAAGACTGAC AAAAAGTACC TGATGATCGA AGAGTATTTG ACCAAAGAGC TGCTGGCCCT GGATTCAGTG   1710
V  D  N  F     E  G  K     K  T  D     K  K  Y  L     M  I  E     E  Y  L     T  K  E  L     L  A  L     D  S  V

GACCCCGAGG GACGAGCCGA TGTGCGTCAG GCCAGGAGAG ACGGTGTCAG GAAGGTTCAG ACCATCTTGG AAAAACTTGA ACAGAAAGCC   1800
D  P  E  G     R  A  D     V  R  Q     A  R  R  D     G  V  R     K  V  Q     T  I  L  E     K  L  E     Q  K  A

ATTGATGTCC CAGGTCAAGT CCAGGTCTAT GAACTCCAGC CCAGCAACCT TGAAGCAGAT CAGCCACTGC AGGCAATCAT GGAGATGGGT   1890
I  D  V  P     G  Q  V     Q  V  Y     E  L  Q  P     S  N  L     E  A  D     Q  P  L  Q     A  I  M     E  M  G

GCCGTGGCAG CAGACAAGGG CAAGAAAAAT GCTGGAAATG CAGAAGATCC CCACACAGAA ACCCAGCAGC CAGAAGCCAC AGCAGCAGCG   1980
A  V  A  A     D  K  G     K  K  N     A  G  N  A     E  D  P     H  T  E     T  Q  Q  P     E  A  T     A  A  A

ACTTCAAACC CCAGCAGCAT GACAGACACC CCTGGTAACC CAGCAGCACC GTAGCCTCTG CCCTGTAAAA GTCAGACTCG GAACCGATGT   2070
T  S  N  P     S  S  M     T  D  T     P  G  N  P     A  A  P  .

GTGCTTTAGG GATTTTAGTT GCATGCATTT CAGAGACTTT AGGTCAGTTG GTTTTGATTA GCTGCTTGGT ATGCAGTACT TGGGTGAGGC   2160
AAACACTATA AAGGGCTAAA AGGGAAAATG ATGCTTTTCT TCAATATTCT TACTCTTGTA CAATTAANGA AGTTGCTTGT TGTTTGAGAA   2250
GTTTAACCCC GTTGCTTGTT CTGCAGCCCT GTCNACTTGG GCACCCCCAC CACCTGTTAG CTGTGGTTGT GCACTGTCTT TTGTAGCTCT   2340
GGACTGGAGG GGTAGATGGG GAGTCAATTA CCCATCACAT AAATATGAAA CATTTATCAG AAATGTTGCC ATTTTAATGA GATGATTTTC   2430
TTCATCTCAT AATTAAAATA CCTGACTTTA GAGAGAGTAA AATGTGCCAG GAGCCATAGG AATATCTGTA TGTTGGATGA CTTTAATGCT   2520
ACATTTTH                                                                                              2528
```

FIG.3

BNSDOCID <WO 0014106A1 IA>

BASDOCID <WO 0014106A1 IA>

```
ACGATATCCT GTAAGACCAA GAATTGCAAG GCCAGAGTTT GAATTCTTAT ACAAATGGAG CGTATGGTCC AACATACCCC CCAGGCCCTG     90
GGGCAAATAC TGCCTCATAC TCAGGGGCTT ATTATGCACC TGGTTATACT CAGACCAGTT ACTCCACAGA AGTTCCAAGT ACTTACCGTT    180
CATCTGGCAA CAGCCCAACT CCAGTCTCTC GTTGGATCTA TCCCCAGCAG GACTGTCAAG ACTGAAGCAC CCCCTCTTAA GGGGCAGGTT    270
CCAGGATATC CGCCTTCACA GAACCCTGGA ATGACCCTGC CCCATTATCC TTATGGAGAT GGTAATCGTA GTGTTCCACA ATCACGGCCG    360
                                                        M  E  M  V  I  V  V  F  H  N  H  G  R
ACTGTACGAC CACAAGAAAG ATGCGTGGGC TTCTCCTGGT GCTTATGGAA TGGGTGGCCG TTATCCCTGG CCTTCATCAG CGCCCTCAGC    450
 L  Y  D  H  K  K  D  A  W  A  S  P  G  A  Y  G  M  G  G  R  Y  P  W  P  S  S  A  P  S  A
ACCACCCGGC AATCTCTACA TGACTGAAAG TACTTCACCA TGGCCTAGCA GTGGCTCTCC CCAGTCACCC CCTTCACCCC CAGTCCAGCA    540
 P  P  G  N  L  Y  M  T  E  S  T  S  P  W  P  S  S  G  S  P  Q  S  P  P  S  P  P  V  Q  Q
GCCCAAGGAT TCTTCATACC CCTATAGCCA ATCAGATCAA AGCATGAACC GGCACAACTT TCCTTGCAGT GTCCATCAGT ACGAATCCTC    630
 P  K  D  S  S  Y  P  Y  S  Q  S  D  Q  S  M  N  R  H  N  F  P  C  S  V  H  Q  Y  E  S  S
GGGGACAGTG AACAATGATG ATTCAGATCT TTTGGATTCC CAAGTCCAGT ATAGTGCTGA GCCTCAGCTG TATGGTAATG CCACCAGTGA    720
 G  T  V  N  N  D  D  S  D  L  L  D  S  Q  V  Q  Y  S  A  E  P  Q  L  Y  G  N  A  T  S  D
CCATCCCAAC AATCAAGATC AAAGTAGCAG TCTTCCTGAA GAATGTGTAC CTTCAGATGA AAGTACTCCT CCGAGTATTA AAAAAATCAT    810
 H  P  N  N  Q  D  Q  S  S  S  L  P  E  E  C  V  P  S  D  E  S  T  P  P  S  I  K  K  I  I
ACATGTGCTG GAGAAGGTCC AGTATCTTGA ACAAGAAGTA GAAGAATTTG TAGGAAAAAA GACAGACAAA GCATACTGGC TTCTGGAAGA    900
 H  V  L  E  K  V  Q  Y  L  E  Q  E  V  E  E  F  V  G  K  K  T  D  K  A  Y  W  L  L  E  E
AATGCTAACC AAGGAACTTT TGGAACTGGA TTCAGTTGAA ACTGGGGGCC AGGACTCTGT ACGGCAGGCC AGAAAAGAGG CTGTTTGTAA    990
 M  L  T  K  E  L  L  E  L  D  S  V  E  T  G  G  Q  D  S  V  R  Q  A  R  K  E  A  V  C  K
GATTCAGGCC ATATTGGAAA                                                                             1010
 I  Q  A  I  L  E
```

FIG. 4

SUBSTITUTE SHEET (RULE 26)

BNSDOCID <WO 0014106A1 IA>

```
GAGAAATAAA AAATGAACTT CTCCAAGCAC AAAACCCTTC TGAATTGTAC CTGAGCTCCA AAACAGAATT GCAGGGTTTA ATTGGACAGT    90
  E  I  K  N  E  L  L  Q  A  Q  N  P  S  E  L  Y  L  S  S  K  T  E  L  Q  G  L  I  G  Q  L

TGGATGAGGT AAGTNTTGAA AAAAACCCCT GCATCCGGGA AGCCAGGAGA AGAGCAGTGA TCGAGGTGCA AACTCTGATC ACATATATTG   180
  D  E  V  S  X  E  K  N  P  C  I  R  E  A  R  R  R  A  V  I  E  V  Q  T  L  I  T  Y  I  D

ACTTGAAGGA GGCCCTTGAG AAAAGAAAGC TGTTTGCTTG TGAGGAGCAC CCATCCCATA AAGCCGTCTG GAACGTCCTT GGAAACTTGT   270
  L  K  E  A  L  E  K  R  K  L  F  A  C  E  E  H  P  S  H  K  A  V  W  N  V  L  G  N  L  S

CTGAGATCCA GGGAGAAGTT CTTTCATTTG ATGGAAATCG AACCGATAAG AACTACATCC GGCTGGAAGA GCTGCTCACC AAGCAGCTGC   360
  E  I  Q  G  E  V  L  S  F  D  G  N  R  T  D  K  N  Y  I  R  L  E  E  L  L  T  K  Q  L  L

TAGCCCTGGA TGCTGTTGAT CCGCAGGGAG AAGAGAAGTG TAAGGCTGCC AGGAAACAAG CTGTGAGGCT TGCGCAGAAT ATTCTCAGCT   450
  A  L  D  A  V  D  P  Q  G  E  E  K  C  K  A  A  R  K  Q  A  V  R  L  A  Q  N  I  L  S  Y

ATCTCGACCT GAAATCTGAT GAATGGGAGT ACTGAAATAC CAGAGATCTC ACTTTTGATA CTGTTTTGCA CTTCATATGT GCTTCTATGT   540
  L  D  L  K  S  D  E  W  E  Y  .

ATAGAGAGCT TTCAGTTCAT TGATTTATAC GTGCATATTT CAGTCTCAGT ATTTATGATT GAAGCAAATT CTATTCAGTA TCTGCTGCTT   630

TTGATGTTGC AAGACAAATA TCATTACAGC ACGTTAACTT TTCCATTCGG ATCAAAAAA                                      689
```

FIG.5

ATGTCTTTCCGCCTCTTCGTTGAAATATTTCACTTTCTTTTCCAGCTTTTTCCCCATCTCGAC
CT
GCTTTGGTTTTT
CGAGAAAACCACGTTCCAAATCAGCGACATCTCTCAAATTGAGATCATAGGCTTTTTGAAGA
TTGCTCAAATTATG
CTTCTCATATTGCATGAGCATTTTGAAGCCCGCGTCATCAACCAAAGCATTTTTTTCCACCCAT
CACAATGATTTTAT CATTTTCTTTAAAATT

FIG. 6A

BNSDOCID <WO__0014106A1_IA>

MKVNVSCSSV	QTTIDILEEN	QGEDESILTL	GQLRDRIATD	NDVDVETMKL	50
LHRGKFLQGA	DDVSLSTLNF	KENDKIIVMG	GKNALVDDAG	FKMLMQYEKH	100
NLSNLQKAYD	LNLRDVADLE	RGFLEKPKQV	EMGKKLEKKV	KYFNEEAERH	150
LETLDGMNII	TETTPENQAK	RNREKRKTLV	NGIQTLLNQN	DALLRRLQEY	200
QSVLNGDIPE					210

FIG.6B

BNSDOCID <WO_ _0014106A1 IA>

ATGCCAGTCG	TGAACATACC	AATCAAAATA	CTTGGTCAGA	ATCAATCACA	50
TAGTCGAAGT	AACTCCTCGT	CTTCTGTTGA	CAACGATCGA	AATCAACCAC	100
CACAGCAGCC	ACCTCAACCG	CAACCACAAC	AGCAATCTCA	GCAACAATAC	150
CAGCAGGCTC	CAAACGTGAA	TACCAATATG	CATCATTCCA	ACGGATTCTC	200
ACCTAACTTC	CCATCTCGTA	GTCCTATTCC	GGACTTTCCC	AGTTTTTCAT	250
CTGGGTTCCC	AAACGATTCT	GAATGGTCTT	CGAATTTCCC	GTCGTTTCCA	300
AATTTCCCAA	GTGGATTCTC	AAATGGAAGT	TCTAATTTCC	CTGATTTTCC	350
AAGATTCGGA	AGAGATGGAG	GACTATCGCC	AAACCCACCG	ATGCAAGGAT	400
ACAGGAGAAG	TCCAACACCA	ACATCAACTC	AATCTCCAAC	TTCTACATTA	450
AGACGCAACT	CTCAGCAGAA	TCAAGCTCCT	CCACAATATT	CTCAGCAACA	500
ACCACAACAA	GCTCAACAAC	GTCAGACAAC	TCCTCCGTCA	ACAAAAGCTT	550
CATCTCGACC	ACCATCTCGT	ACTCGTGAAC	CAAAGGAACC	TGAGGTACCC	600
GAGAGACCAG	CAGTTATTCC	ATTGCCATAT	GAGAAGAAGG	AGAAACCACT	650
GGAGAAGAAA	GGTAGTCGTG	ATTCTGGAAA	GGGTGATGAG	AACCTTGAAG	700
AGAACATTGC	CAAGATCACG	ATCGGAAAGA	ATAATTGCGA	GTTATGTCCG	750
GAACAAGAAA	CGGACGGCGA	CCCATCTCCA	CTAACCTCCC	CAATCACCGA	800
AGGAAAGCCA	AAGAGAGGAA	AGAAACTTCA	ACGTAATCAA	AGTGTTGTTG	850
ATTTCAATGC	CAAGACAATT	GTTACTTTGG	ATAAAATTGA	ATTACAAGTT	900
GAGCAGTTGA	GAAAAAAAGC	TGCTGAACTC	GAAATGGAAA	AAGAGCAAAT	950
TCTTCGTTCT	CTAGGAGAAA	TCAGTGTTCA	TAACTGCATG	TTCAAACTGG	1000
AAGAATGTGA	TCGTGAAGAG	ATTGAAGCAA	TCACTGACCG	ATTGACAAAA	1050
AGAACAAAGA	CAGTTCAAGT	TGTTGTCGAA	ACTCCACGAA	ATGAAGAACA	1100
GAAAAAAGCA	CTGGAAGATG	CAACTTTGAT	GATCGATGAA	GTCGGAGAAA	1150
TGATGCATTC	GAATATTGAA	AAGGCTAAGC	TGTGCCTACA	AACCTACATG	1200
AACGCCTGTT	CGTACGAAGA	AACTGCTGGA	GCCACCTGCC	AAAACTTCTT	1250
GAAGATCATA	ATTCAGTGCG	CTGCTGATGA	TCAGAAACGC	ATCAAGCGTC	1300
GTCTGGAAAA	TCTGATGTCT	CAAATTGAGA	ATGCTGAGAG	AACGAAAGCA	1350
GATTTGATGG	ATGATCAAAG	CGAATAG			1377

FIG.7A

BNSDOCID <WC_ 0014106A1 >A>

MPVVNIPIKI	LGQNQSHSRS	NSSSSVDNDR	NQPPQQPPQP	QPQQQSQQQY	50
QQAPNVNTNM	HHSNGFSPNF	PSRSPIPDFP	SFSSGFPNDS	EWSSNFPSFP	100
NFPSGFSNGS	SNFPDFPRFG	RDGGLSPNPP	MQGYRRSPTP	TSTQSPTSTL	150
RRNSQQNQAP	PQYSQQQPQQ	AQQRQTTPPS	TKASSRPPSR	TREPKEPEVP	200
ERPAVIPLPY	EKKEKPLEKK	GSRDSGKGDE	NLEENIAKIT	IGKNNCELCP	250
EQETDGDPSP	LTSPITEGKP	KRGKKLQRNQ	SVVDFNAKTI	VTLDKIELQV	300
EQLRKKAAEL	EMEKEQILRS	LGEISVHNCM	FKLEECDREE	IEAITDRLTK	350
RTKTVQVVVE	TPRNEEQKKA	LEDATLMIDE	VGEMMHSNIE	KAKLCLQTYM	400
NACSYEETAG	ATCQNFLKII	IQCAADDQKR	IKRRLENLMS	QIENAERTKA	450
DLMDDQSE					458

FIG.7B

BNSDOCID <WO 0014106A1 IA>

ATGTCAGAAA	AGACTAGCAC	AGTTACAATA	CACTATGGAA	ATCAGCGATT	50
TCCGGTAGCA	GTCAATCTAA	ATGAGACGTT	AAGTGAACTG	ATTGATGATT	100
TACTTGAAAC	GACTGAGATT	TCTGAGAAGA	AAGTCAAGCT	TTTTTACGCT	150
GGCAAGCGTT	TAAAAGACAA	AAAAGCCTCG	TTATCAAAAT	TGGGTTTAAA	200
AAATCATAGT	AAAATTCTAT	GTATAAGACC	ACATAAGCAA	CAACGAGGTT	250
CCAAGGAAAA	AGACACGGTT	GAGCCCGCTC	CGAAAGCGGA	AGCGGAGAAT	300
CCTGTATTTT	CGCGTATTTC	TGGAGAAATA	AAAGCCATCG	ATCAGTATGT	350
TGACAAAGAA	CTTTCCCCCA	TGTACGACAA	TTACGTAAAT	AAACCGTCGA	400
ACGATCCAAA	GCAGAAAAAC	AAACAGAAAC	TAATGATAAG	TGAACTACTT	450
TTACAACAGC	TTTTAAAATT	GGATGGAGTT	GACGTACTGG	GCAGCGAGAA	500
ATTGCGTTTT	GAACGGAAGC	AACTTGTTTC	TAAGATCCAA	AAAATGTTGG	550
ATCACGTTGA	CCAAACAAGC	CAAGAAGTGG	CCGCATAG		588

FIG. 8A

BNSDOCID <WO 0014106A1 A>

MSEKTSTVTI	HYGNQRFPVA	VNLNETLSEL	IDDLLETTEI	SEKKVKLFYA	50
GKRLKDKKAS	LSKLGLKNHS	KILCIRPHKQ	QRGSKEKDTV	EPAPKAEAEN	100
PVFSRISGEI	KAIDQYVDKE	LSPMYDNYVN	KPSNDPKQKN	KQKLMISELL	150
LQQLLKLDGV	DVLGSEKLRF	ERKQLVSKIQ	KMLDHVDQTS	QEVAA	195

FIG.8B

BNSDOCID <WO 0014106A1 IA>

ATGTCTTTTT	TTACCCAGTT	GTGTTCTATG	GATAAAAAAT	ATTGGATCTC	50
TCTAGCTGTA	TTGTCAGTTA	CTGTTTTGAT	TAGCGCATTA	TTGAAAAAGA	100
GAGCTACTGA	AACCGAAGAT	ATTGTCGTTG	TTCATTACGA	TGGCGAAAAG	150
TTGAATTTTG	TGTTGCGACA	ACCAAGGCTG	AATATGGTTT	CTTACACTAG	200
TTTTCTTCGT	CGCGTGTGCA	ACGCATTTTC	AGTAATGCCC	GACAAAGCGT	250
CTCTCAAGTT	AAACGGGGTG	ACCCTCAAGG	ATGGTTCACT	TTCCGACCAA	300
AATGTGCAAA	ATGGAAGTGA	ATTAGAGCTC	GAATTACCCA	AACTGAGCCC	350
GGCAATGCAA	CAAATTGAAG	CATATATAGA	TGAGCTTCAA	CAGGATCTCG	400
TCCCTAAAAT	TGAAGCCTTC	TGCCAATCGT	CTCCCGCTTC	GGCACAAGAT	450
GTTCAAGATT	TGCATACACG	CCTTAGTGAA	ACATTGTTGG	CTAGGATGAT	500
AAAATTAGAT	GCTGTTAATG	TTGAAGACGA	CCCAGAAGCT	CGTCTTAAAA	550
GAAAAGAAGC	TATTCGTTTA	TCTCAACAAT	ATTTGAGTAA	ACTAGATTCC	600
ACCAAGAATC	AAAACAAATG	A			621

FIG. 9A

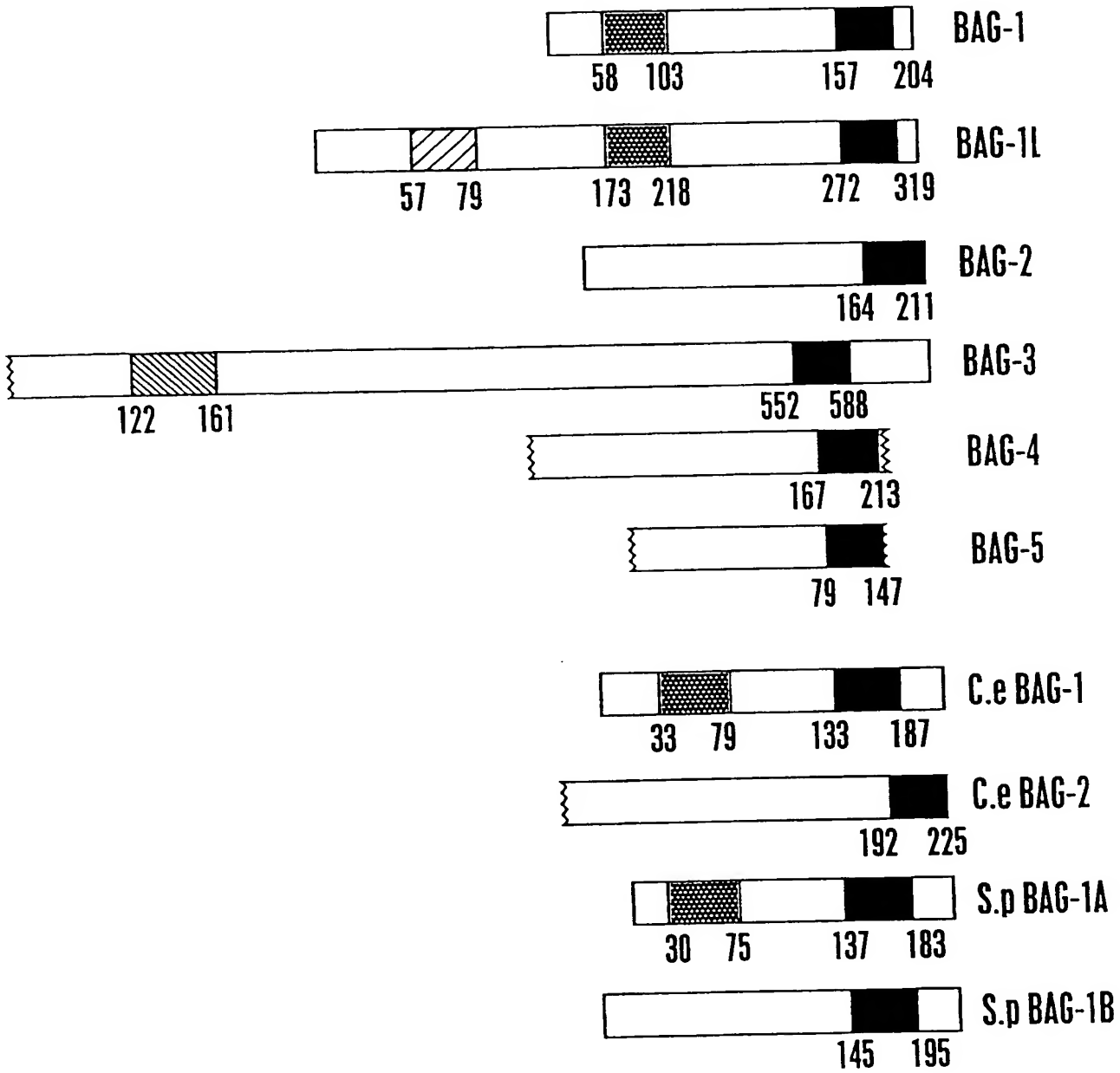
BNSDOCID <WO 0014106A1_IA>

MSFFTQLCSM	DKKYWISLAV	LSVTVLISAL	LKKRATETED	IVVVHYDGEK	50
LNFVLRQPRL	NMVSYTSFLR	RVCNAFSVMP	DKASLKLNGV	TLKDGSLSDQ	100
NVQNGSELEL	ELPKLSPAMQ	QIEAYIDELQ	QDLVPKIEAF	CQSSPASAQD	150
VQDLHTRLSE	TLLARMIKLD	AVNVEDDPEA	RLKRKEAIRL	SQQYLSKLDS	200
TKNQNK					206

FIG.9B

BNSDOCID <WO 0014106A1 IA>

Fig.10A



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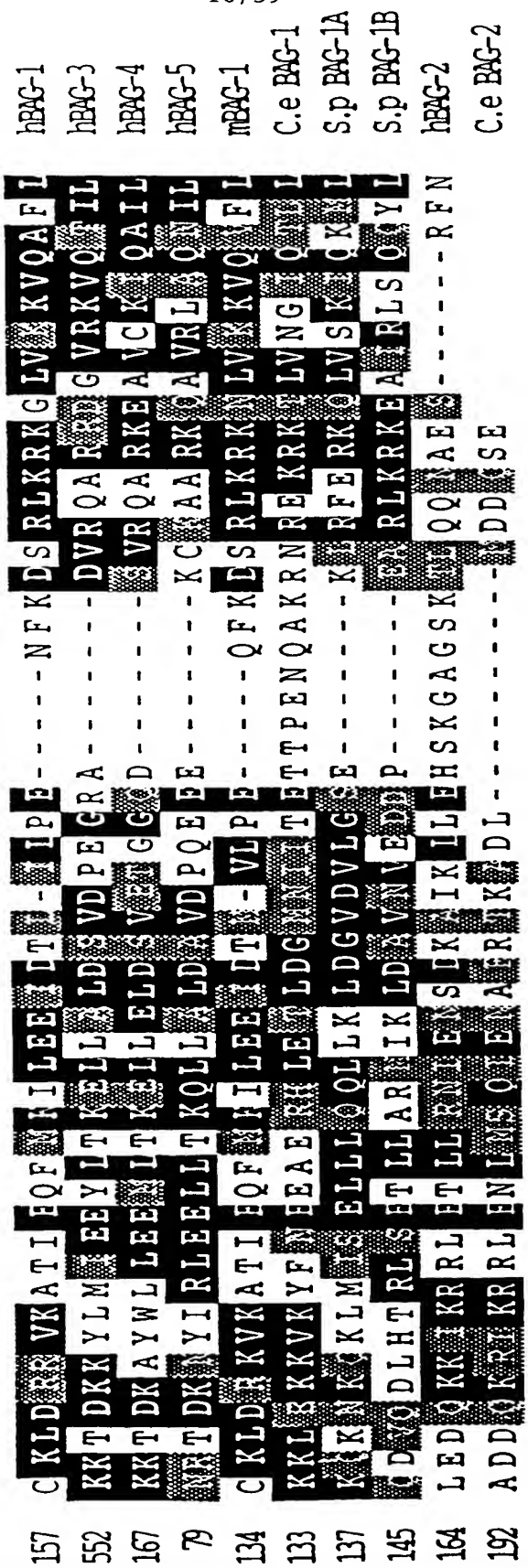
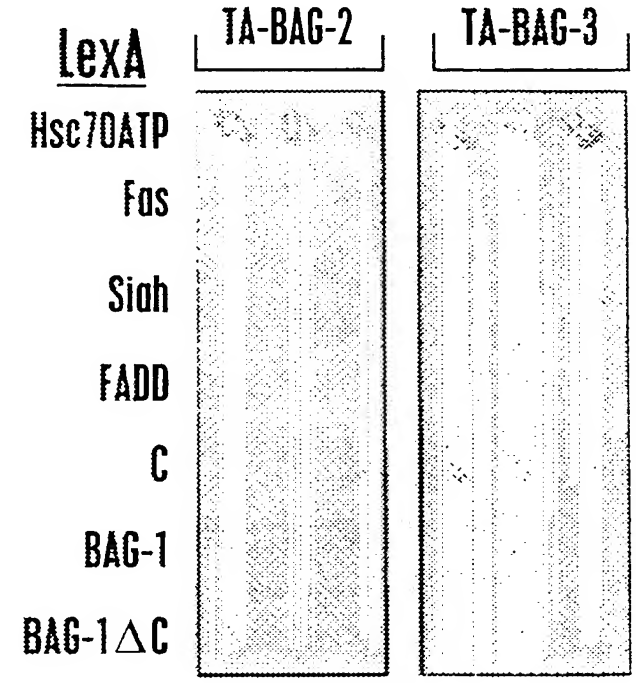


Fig.10B

BNSDOCID <WO 0014106A1 IA>



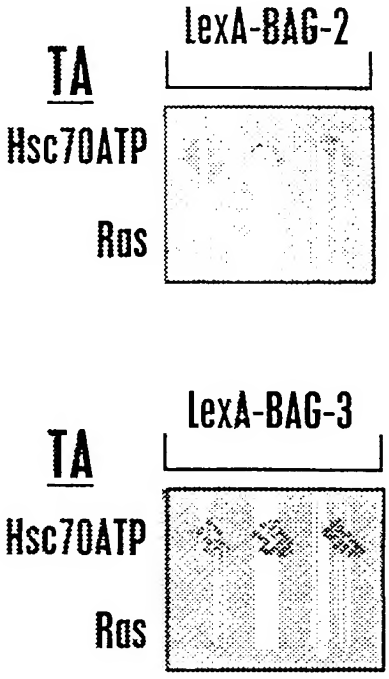


Fig. 11B

Fig. 11A

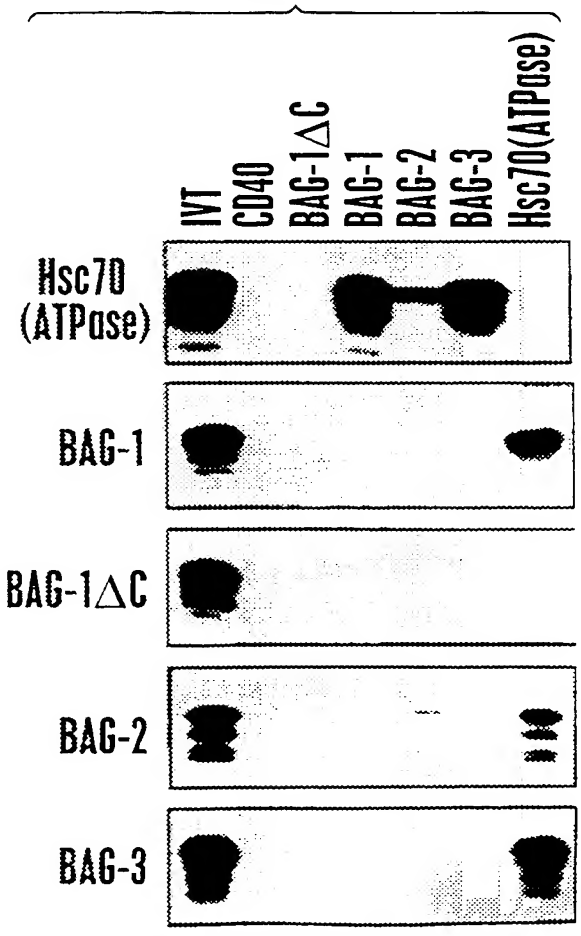


Fig. 11C

BNSDOCID <WO 0014106A1 IA>

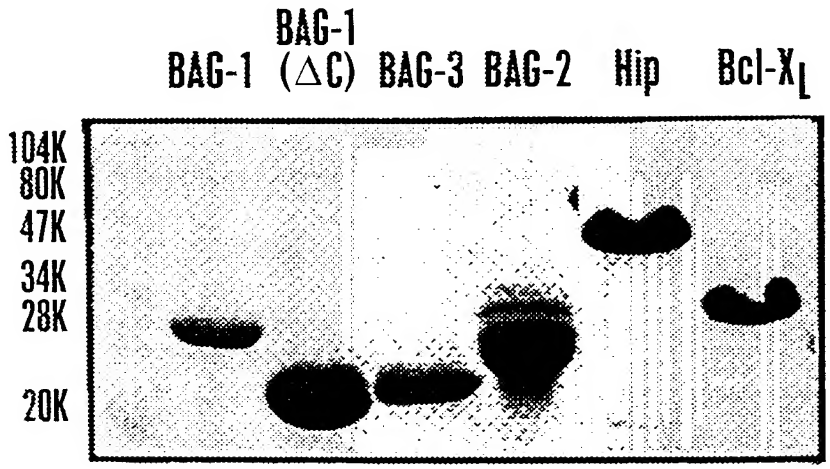


Fig. 12

BNSDOCID <WO 0014106A1 IA>

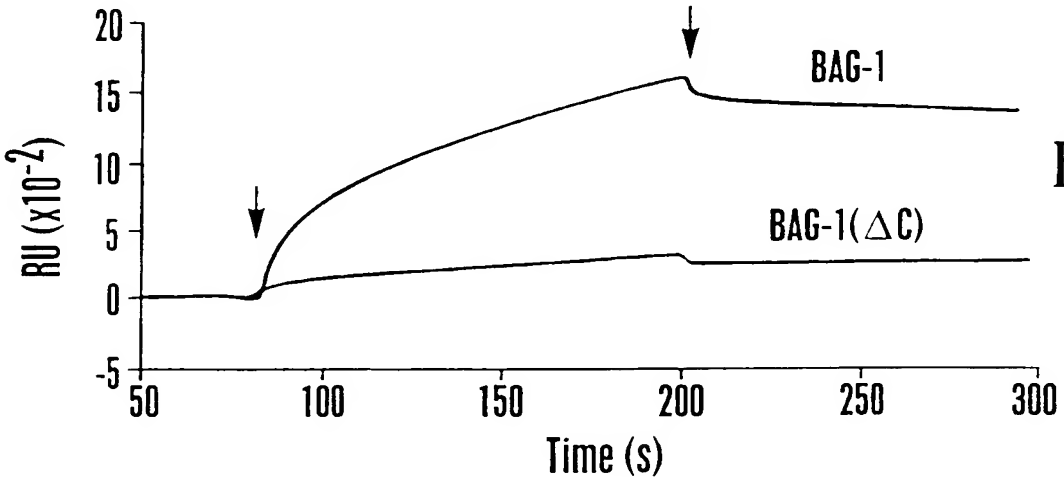


Fig. 13A

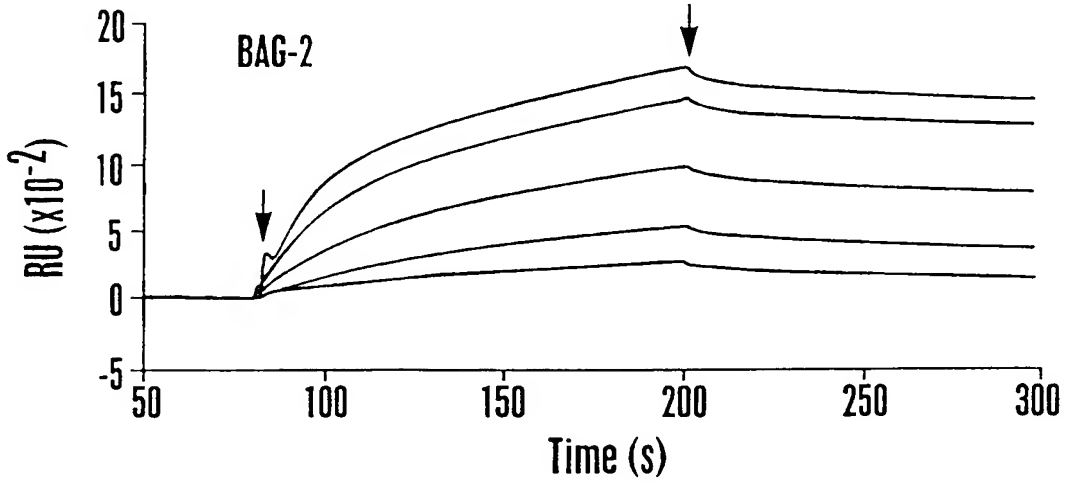


Fig. 13B

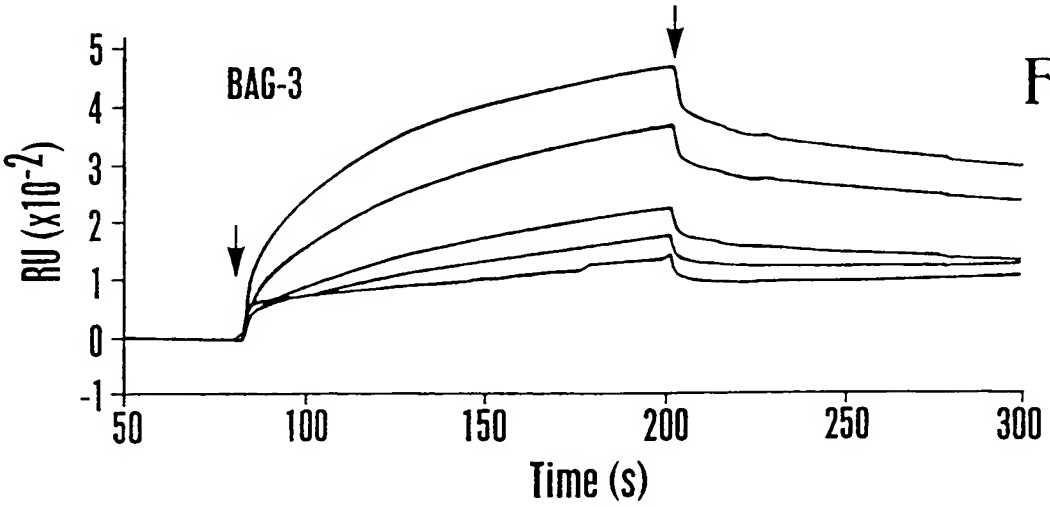


Fig. 13C

BNSDOCID <WO 0014106A1 I A>

Fig. 14A

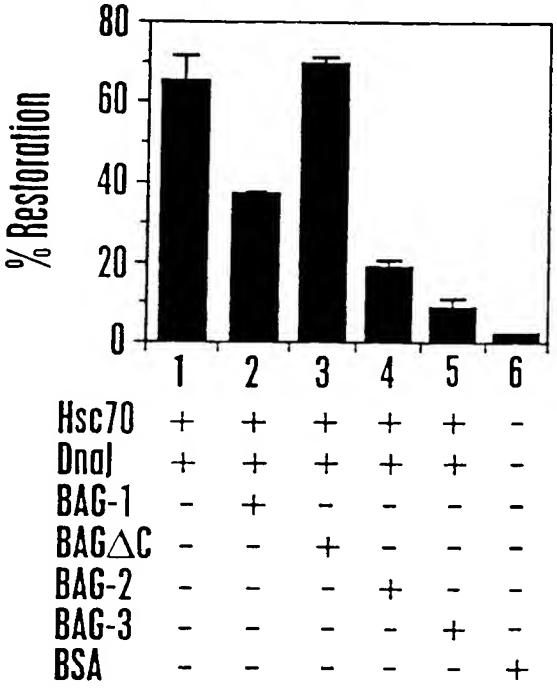


Fig. 14B

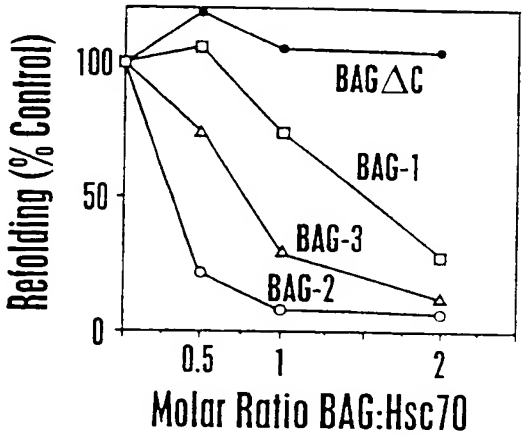
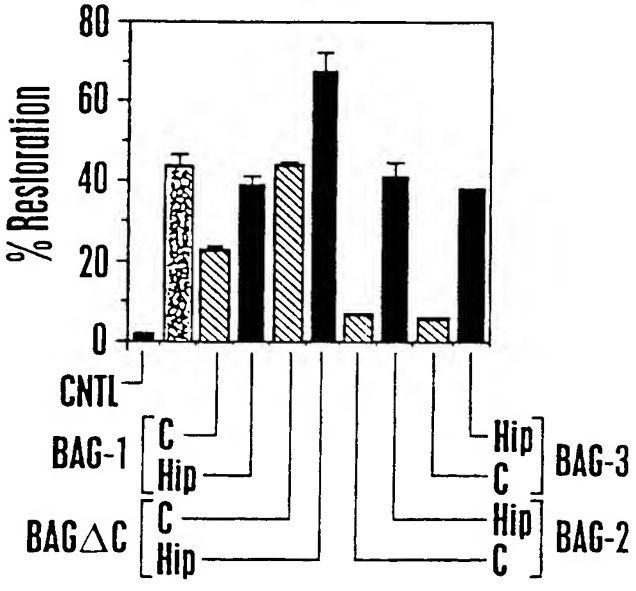


Fig. 14C



BNSDOCID <WC 0014106A1 IA>

FIG. 15A

GCGGAGCTCC GCATCCAACC CCGGGCCGCG GCCAACTTCT CTGGACTGGA 50
CCAGAAGTTT CTAGCCGGCC AGTTGCTACC TCCCTTTATC TCCTCCTTCC 100
CCTCTGGCAG CGAGGAGGCT ATTTCCAGAC ACTTCCACCC CTCTCTGGCC 150
ACGTCACCCC CGCCTTTAAT TCATAAAGGT GCCCGGCGCC GGCTTCCCGG 200
ACACGTCGGC GGCGGAGAGG GGCCCACGGC GGCGGCCCGG CCAGAGACTC 250
GGCGCCCCGA GCCAGCGCCC CGCACCCGCG CCCCAGCGGG CAGACCCCAA 300
CCCAGCATGA GCGCCGCCAC CCACTCGCCC ATGATGCAGG TGGCGTCCGG 350
CAACGGTGAC CGCGACCCTT TGCCCCCCGG ATGGGAGATC AAGATCGACC 400
CGCAGACCGG CTGGCCCTTC TTCGTGGACC ACAACAGCCG CACCACTACG 450
TGGAACGACC CGCGCGTGCC CTCTGAGGGC CCCAAGGAGA CTCCATCCTC 500
TGCCAATGGC CCTTCCCGGG AGGGCTCTAG GCTGCCGCCT GCTAGGGAAG 550
GCCACCCCTG TGTACCCCCAG CTCCGACCAG GCTACATTCC CATTCCTGTG 600
CTCCATGAAG GCGCTGAGAA CCGGCAGGTG CACCCTTTCC ATGTCTATCC 650
CCAGCCTGGG ATGCAGCGAT TCCGAACTGA GGCGGCAGCA GCGGCTCCTC 700
AGAGGTCCCA GTCACCTCTG CGGGGCATGC CAGAAACCAC TCAGCCAGAT 750
AAACAGTGTG GACAGGTGGC AGCGGCGGCG GCAGCCCAGC CCCCAGCCTC 800
CCACGGACCT GAGCGGTCCC AGTCTCCAGC TGCCTCTGAC TGCTCATCCT 850
CATCCTCCTC GGCCAGCCTG CCTTCCTCCG GCAGGAGCAG CCTGGGCAGT 900
CACCAGCTCC CGCGGGGGTA CATCTCCATT CCGGTGATAC ACGAGCAGAA 950
CGTTACCCGG CCAGCAGCCC AGCCCTCCTT CCACAAAGCC CAGAAGACGC 1000
ACTACCCAGC GCAGAGGGGT GAGTACCAGA CCCACCAGCC TGTGTACCAC 1050
AAGATCCAGG GGGATGACTG GGAGCCCCCG CCCCTGCGGG CGGCATCCCC 1100
GTTCAGGTCA TCTGTCCAGG GTGCATCGAG CCGGGAGGGC TCACCAGCCA 1150
GGAGCAGCAC GCCACTCCAC TCCCCCTCGC CCATCCGTGT GCACACCGTG 1200
GTCGACAGGC CTCAGCAGCC CATGACCCAT CGAGAAACTG CACCTGTTTC 1250
CCAGCCTGAA AACAAACCAG AAAGTAAGCC AGGCCCAGTT GGACCAGAAC 1300
TCCCTCCTGG ACACATCCCA ATTCAAGTGA TCCGCAAAGA GGTGGATTCT 1350

BNSDOCID <WO 0014106A1 IA>

FIG.15B

AAACCTGTTT CCCAGAAGCC CCCACCTCCC TCTGAGAAGG TAGAGGTGAA 1400
AGTTCCCCCT GCTCCAGTTC CTTGTCCTCC TCCCAGCCCT GGCCCTTCTG 1450
CTGTCCCCTC TTCCCCCAAG AGTGTGGCTA CAGAAGAGAG GGCAGCCCCC 1500
AGCACTGCCC CTGCAGAAGC TACACCTCCA AAACCAGGAG AAGCCGAGGC 1550
TCCCCCAAAA CATCCAGGAG TGCTGAAAGT GGAAGCCATC CTGGAGAAGG 1600
TGCAGGGGCT GGAGCAGGCT GTAGACAACT TTGAAGGCAA GAAGACTGAC 1650
AAAAAGTACC TGATGATCGA AGAGTATTTG ACCAAAGAGC TGCTGGCCCT 1700
GGATTCAGTG GACCCCGAGG GACGAGCCGA TGTGCGTCAG GCCAGGAGAG 1750
ACGGTGTCAG GAAGGTTCAG ACCATCTTGG AAAAACTTGA ACAGAAAGCC 1800
ATTGATGTCC CAGGTCAAGT CCAGGTCTAT GAACTCCAGC CCAGCAACCT 1850
TGAAGCAGAT CAGCCACTGC AGGCAATCAT GGAGATGGGT GCCGTGGCAG 1900
CAGACAAGGG CAAGAAAAAT GCTGGAAATG CAGAAGATCC CCACACAGAA 1950
ACCCAGCAGC CAGAAGCCAC AGCAGCAGCG ACTTCAAACC CCAGCAGCAT 2000
GACAGACACC CCTGGTAACC CAGCAGCACC GTAGCCTCTG CCCTGTAAAA 2050
ATCAGACTCG GAACCGATGT GTGCTTTAGG GAATTTTAAG TTGCATGCAT 2100
TTCAGAGACT TTAAGTCAGT TGGTTTTTAT TAGCTGCTTG GTATGCAGTA 2150
ACTTGGGTGG AGGCAAAACA CTAATAAAAG GGCTAAAAAG GAAAATGATG 2200
CTTTTCTTCT ATATTCTTAC TCTGTACAAA TAAAGAAGTT GCTTGTTGTT 2250
TGAGAAGTTT AACCCCGTTG CTTGTTCTGC AGCCCTGTCT ACTTGGGCAC 2300
CCCCACCACC TGTTAGCTGT GGTTGTGCAC TGTCTTTTGT AGCTCTGGAC 2350
TGGAGGGGTA GATGGGGAGT CAATTACCCA TCACATAAAT ATGAAACATT 2400
TATCAGAAAT GTTGCCATTT TAATGAGATG ATTTTCTTCA TCTCATAATT 2450
AAAATACCTG ACTTTAGAGA GAGTAAAATG TGCCAGGAGC CATAGGAATA 2500
TCTGTATGTT GGATGACTTT AATGCTACAT TTTC 2534

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FIG. 15C

MSAATHSPMM QVASGNGDRD PLPPGWEIKI DPQTGWPFFV DHNSRTTTWN 50
DPRVPSEGPK ETPSSANGPS REGSRLPPAR EGHPVYPQLR PGYIPIPVLH 100
EGAENRQVHP FHVYPQPGMQ RFRTEAAAAA PQRSQSPLRG MPETTQPDKQ 150
CGQVAAAAAA QPPASHGPER SQSPAASDCS SSSSSASLPS SGRSSLGSHQ 200
LPRGYISIPV IHEQNVTRPA AQPSFHKAQK THYPAQRGEY QTHQPVYHKI 250
QGDDWEPRPL RAASPFRSSV QGASSREGSP ARSSTPLHSP SPIRVHTVVD 300
RPQQPMTHRE TAPVSQPENK PESKPGPVGP ELPPGHIPIQ VIRKEVDSKP 350
VSQKPPPPSE KVEVKVPPAP VPCPPPSPGP SAVPSSPKSV ATEERAAPST 400
APAEATPPKP GEAEAPPKHP GVLKVEAILE KVQGLEQAVD NFEGKKTDKK 450
YLMIEEYLTK ELLALDSVDP EGRADVRQAR RDGVRKVQTI LEKLEQKAID 500
VPGQVQVYEL QPSNLEADQP LQAIMEMGAV AADKGKKNAG NAEDPHTETQ 550
QPEATAAATS NPSSMTDTPG NPAAP
575

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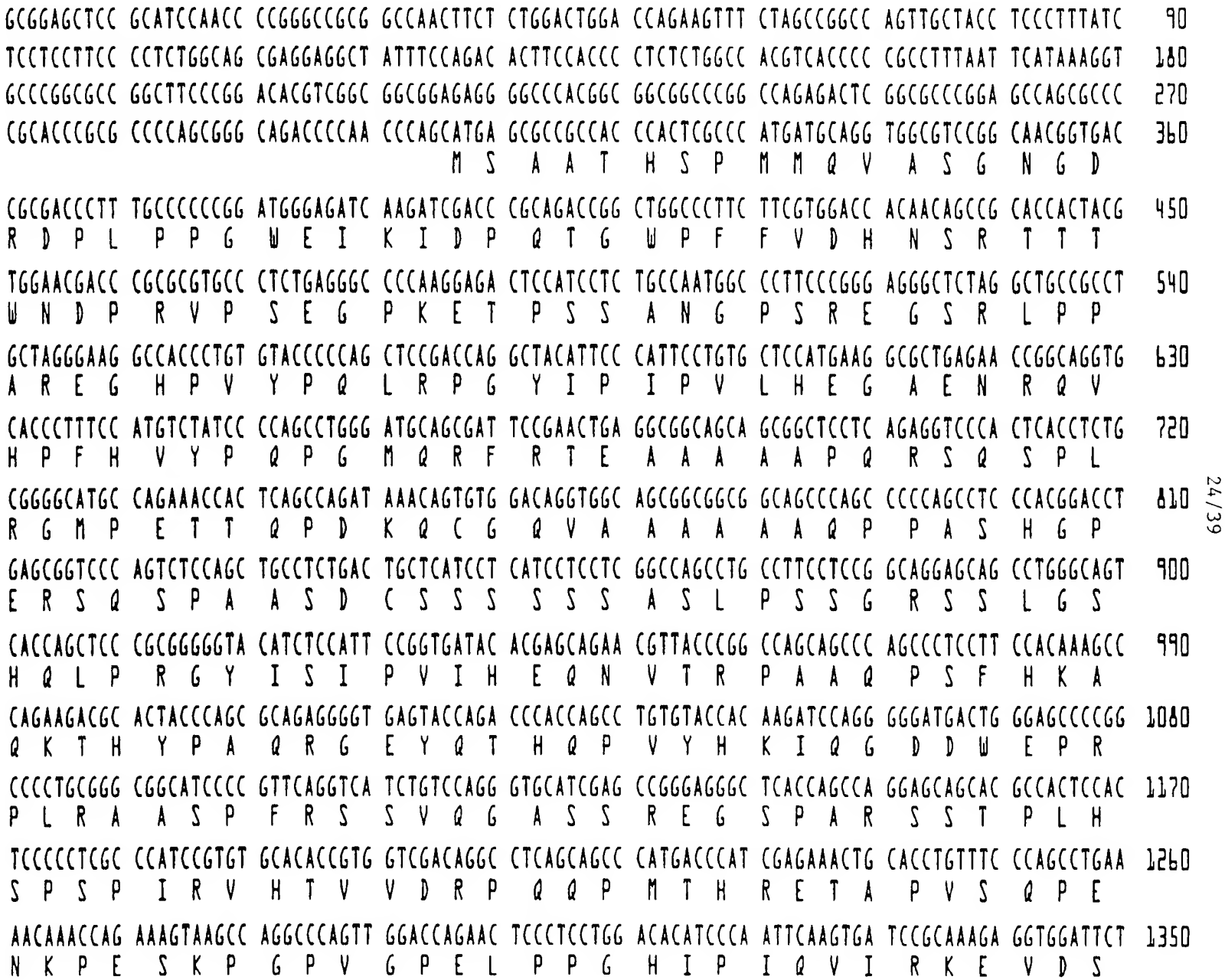

Fig.15D

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BNSDOCID <WO 0014106A1_IA>

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AAACCTGTTT CCCAGAAGCC CCCACCTCCC TCTGAGAAGG TAGAGGTGAA AGTTCCCCCT GCTCCAGTTC CTTGTCCTCC TCCCAGCCCT  1440
K  P  V  S  Q  K  P  P  P  P  S  E  K  V  E  V  K  V  P  P  A  P  V  P  C  P  P  P  S  P

GGCCCTTCTG CTGTCCCCTC TTCCCCCAAG AGTGTGGCTA CAGAAGAGAG GGCAGCCCCC AGCACTGCCC CTGCAGAAGC TACACCTCCA  1530
G  P  S  A  V  P  S  S  P  K  S  V  A  T  E  E  R  A  A  P  S  T  A  P  A  E  A  T  P  P

AAACCAGGAG AAGCCGAGGC TCCCCCAAAA CATCCAGGAG TGCTGAAAGT GGAAGCCATC CTGGAGAAGG TGCAGGGGCT GGAGCAGGCT  1620
K  P  G  E  A  E  A  P  P  K  H  P  G  V  L  K  V  E  A  I  L  E  K  V  Q  G  L  E  Q  A

GTAGACAACT TTGAAGGCAA GAAGACTGAC AAAAAGTACC TGATGATCGA AGAGTATTTG ACCAAAGAGC TGCTGGCCCT GGATTCAGTG  1710
V  D  N  F  E  G  K  K  T  D  K  K  Y  L  M  I  E  E  Y  L  T  K  E  L  L  A  L  D  S  V

GACCCCGAGG GACGAGCCGA TGTGCGTCAG GCCAGGAGAG ACGGTGTCAG GAAGGTTCAG ACCATCTTGG AAAAACTTGA ACAGAAAGCC  1800
D  P  E  G  R  A  D  V  R  Q  A  R  R  D  G  V  R  K  V  Q  T  I  L  E  K  L  E  Q  K  A

ATTGATGTCC CAGGTCAAGT CCAGGTCTAT GAACTCCAGC CCAGCAACCT TGAAGCAGAT CAGCCACTGC AGGCAATCAT GGAGATGGGT  1890
I  D  V  P  G  Q  V  Q  V  Y  E  L  Q  P  S  N  L  E  A  D  Q  P  L  Q  A  I  M  E  M  G

GCCGTGGCAG CAGACAAGGG CAAGAAAAAT GCTGGAAATG CAGAAGATCC CCACACAGAA ACCCAGCAGC CAGAAGCCAC AGCAGCAGCG  1980
A  V  A  A  D  K  G  K  K  N  A  G  N  A  E  D  P  H  T  E  T  Q  Q  P  E  A  T  A  A  A

ACTTCAAACC CCAGCAGCAT GACAGACACC CCTGGTAACC CAGCAGCACC CTAGCCTCTG CCCTGTAAAA ATCAGACTCG GAACCGATGT  2070
T  S  N  P  S  S  M  T  D  T  P  G  N  P  A  A  P

GTGCTTTAGG GAATTTTAAG TTGCATGCAT TTCAGAGACT TTAAGTCAGT TGGTTTTTAT TAGCTGCTTG GTATGCAGTA ACTTGGGTGG  2160
AGGCAAAACA CTAATAAAAG GGCTAAAAAG GAAAATGATG CTTTTCTTCT ATATTCTTAC TCTGTACAAA TAAAGAAGTT GCTTGTTGTT  2250
TGAGAAGTTT AACCCCGTTG CTTGTTCTGC AGCCCTGTCT ACTTGGGCAC CCCCACCACC TGTTAGCTGT GGTTGTGCAC TGTCTTTTGT  2340
AGCTCTGGAC TGGAGGGGTA GATGGGGAGT CAATTACCCA TCACATAAAT ATGAAACATT TATCAGAAAT GTTGCCATTT TAATGAGATG  2430
ATTTTCTTCA TCTCATAATT AAAATACCTG ACTTTAGAGA GAGTAAAATG TGCCAGGAGC CATAGGAATA TCTGTATGTT GGATGACTTT  2520
AATGCTACAT TTTC
```

Fig.15E

FIG. 16A

```
CGGTGGGAGC GGGGCGGGAA GCGCTTCAGG GCAGCGGATC CCATGTCGGC     50
CCTGAGGCGC TCGGGCTACG GCCCCAGTGA CGGTCCGTCC TACGGCCGCT    100
ACTACGGGCC TGGGGGTGGA GATGTGCCGG TACACCCACC TCCACCCTTA    150
TATCCTCTTC GCCCTGAACC TCCCCAGCCT CCCATTTCCT GGCGGGTGCG    200
CGGGGGCGGC CCGGCGGAGA CCACCTGGCT GGGAGAAGGC GGAGGAGGCG    250
ATGGCTACTA TCCCTCGGGA GGCGCCTGGC CAGAGCCTGG TCGAGCCGGA    300
GGAAGCCACC AGGAGCAGCC ACCATATCCT AGCTACAATT CTAACTATTG    350
GAATTCTACT GCGAGATCTA GGGCTCCTTA CCCAAGTACA TATCCTGTAA    400
GACCAGAATT GCAAGGCCAG AGTTTGAATT CTTATACAAA TGGAGCGTAT    450
GGTCCAACAT ACCCCCCAGG CCCTGGGGCA AATACTGCCT CATACTCAGG    500
GGCTTATTAT GCACCTGGTT ATACTCAGAC CAGTTACTCC ACAGAAGTTC    550
CAAGTACTTA CCGTTCATCT GGCAACAGCC CAACTCCAGT CTCTCGTTGG    600
ATCTATCCCC AGCAGGACTG TCAGACTGAA GCACCCCCCTC TTAGGGGGCA    650
GGTTCCAGGA TATCCGCCTT CACAGAACCC TGGAATGACC CTGCCCCCATT    700
ATCCTTATGG AGATGGTAAT CGTAGTGTTC CACAATCAGG ACCGACTGTA    750
CGACCACAAG AAGATGCGTG GGCTTCTCCT GGTGCTTATG GAATGGGTGG    800
CCGTTATCCC TGGCCTTCAT CAGCGCCCTC AGCACCACCC GGCAATCTCT    850
ACATGACTGA AAGTACTTCA CCATGGCCTA GCAGTGGCTC TCCCCAGTCA    900
CCCCCTTCAC CCCCAGTCCA GCAGCCCAAG GATTCTTCAT ACCCCTATAG    950
CCAATCAGAT CAAAGCATGA ACCGGCACAA CTTTCCTTGC AGTGTCCATC   1000
AGTACGAATC CTCGGGGACA GTGATCAATG AAGATTCAGA TCTTTTGGAT   1050
TCCCAAGTCC AGTATAGTGC TGAGCCTCAG CTGTATGGTA ATGCCACCAG   1100
TGACCATCCC AACAATCAAG ATCAAAGTAG CAGTCTTCCT GAAGAATGTG   1150
TACCTTCAGA TGAAAGTACT CCTCCGAGTA TTAAAAAAAT CATACATGTG   1200
CTGGAGAAGG TCCAGTATCT TGAACAAGAA GTAGAAGAAT TTGTAGGAAA   1250
AAAGACAGAC AAAGCATACT GGCTTCTGGA AGAAATGCTA ACCAAGGAAC   1300
```


BNSDOCID <WO 0014106A1 IA>

FIG. 16B

TTTTGGAACT GGATTCAGTT GAAACTGGGG GCCAGGACTC TGTACGGCAG 1350
GCCAGAAAAG AGGCTGTTTG TAAGATTCAG GCCATACTGG AAAAATTAGA 1400
AAAAAAAGGA TTATGAAAGG ATTTAGAACA AAGTGGAAGC CTGTTACTAA 1450
CTTGACCAAA GAACACTTGA TTAGGTTAAT TACCCTCTTT TTGAAATGCC 1500
TGTTGATGAC AAGAAGCAAT ACATTCCAGC TTTTCCTTTG ATTTTATACT 1550
TGAAAAACTG GCAAAGGAAT GGAAGAATAT TTTAGTCATG AAGTTGTTTT 1600
CAGTTTTCAGA CGAATGAATG TAATAGGAAA CTATGGAGTT ACCAATATTG 1650
CCAAGTAGAC TCACTCCTTA AAAAATTTAT GGATATCTAC AAGCTGCTTA 1700
TTACCAGCAG GAGGGAAACA CACTTCACAC AACAGGCTTA TCAGAAACCT 1750
ACCAGATGAA ACTGGATATA ATTTGAGACA AACAGGATGT GTTTTTTTAA 1800
ACATCTGGAT ATCTTGTCAC ATTTTTGTAC ATTGTGACTG CTTTCAACAT 1850
ATACTTCATG TGTAATTATA GCTTAGACTT TAGCCTTCTT GGACTTCTGT 1900
TTTGTTTTGT TATTTGCAGT TTACAAATAT AGTATTATTC TCTAAAAAAA 1950
AAAAAAAAAA AAAAAA 1966

BNSDOCID <WO 0014106A1 IA>

FIG. 16C

MSALRRSGYGPSDGPSYGRYYGPGGGDVPVHPPPPLYPLRPEPPQPPISWRVRGGGPAETTWLGEGGGGDGYYPSGGAWP
EPGRAGGSHQEQPPYPSYNSNYWNSTARSRAPYPSTYPVRPELQGQSLNSYTNGAYGPTYPPGPGANTASYSGAYYAPGY
TQTSYSTEVPSTYRSSGNSPTPVSRWMYPQQDCQTEAPPLRGQVPGYPPSQNPGMTLPHYPYGDGNRSVPQSGPTVRPQE
DAWASPGAYGMGGRYPWPSSAPSAPPGNLYMTESTSPWPSSGSPQSPPSPPVCQPKDSSYPYSQSDQSMNRHNFPCSVHQ
YESSGTVINEDSDLLDSQVQYSAEPQLYGNATSDHPNNQDQSSSLPEECVPSDESTPPSIKKIIHMLEKVQYLEQEVEEF
VGKKTDKAYWLLEEMLTKELLELDSVETGGQDSVRQARKEAVCKIQAILEKLEKKGL

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SNSDOCID <WO 0014106A1 >A>

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CGGTGGGAGC GGGGCGGGAA GCGCTTCAGG GCAGCGGATC CCATGTCGGC CCTGAGGCGC TCGGGCTACG GCCCCAGTGA CGGTCCGTCC      90
                                              M  S  A  L  R  R  S  G  Y  G  P  S  D  G  P  S

TACGGCCGCT ACTACGGGCC TGGGGGTGGA GATGTGCCGG TACACCCACC TCCACCCTTA TATCCTCTTC GCCCTGAACC TCCCCAGCCT     180
Y  G  R  Y  Y  G  P  G  G  G  D  V  P  V  H  P  P  P  P  L  Y  P  L  R  P  E  P  P  Q  P

CCCATTTCCT GGCGGGTGCG CGGGGGCGGC CCGGCGGAGA CCACCTGGCT GGGAGAAGGC GGAGGAGGCG ATGGCTACTA TCCCTCGGGA     270
P  I  S  W  R  V  R  G  G  G  P  A  E  T  T  W  L  G  E  G  G  G  G  D  G  Y  Y  P  S  G

GGCGCCTGGC CAGAGCCTGG TCGAGCCGGA GGAAGCCACC AGGAGCAGCC ACCATATCCT AGCTACAATT CTAACTATTG GAATTCTACT     360
G  A  W  P  E  P  G  R  A  G  G  S  H  Q  E  Q  P  P  Y  P  S  Y  N  S  N  Y  W  N  S  T

GCGAGATCTA GGGCTCCTTA CCCAAGTACA TATCCTGTAA GACCAGAATT GCAAGGCCAG AGTTTGAATT CTTATACAAA TGGAGCGTAT     450
A  R  S  R  A  P  Y  P  S  T  Y  P  V  R  P  E  L  Q  G  Q  S  L  N  S  Y  T  N  G  A  Y

GGTCCAACAT ACCCCCCAGG CCCTGGGGCA AATACTGCCT CATACTCAGG GGCTTATTAT GCACCTGGTT ATACTCAGAC CAGTTACTCC     540
G  P  T  Y  P  P  G  P  G  A  N  T  A  S  Y  S  G  A  Y  Y  A  P  G  Y  T  Q  T  S  Y  S

ACAGAAGTTC CAAGTACTTA CCGTTCATCT GGCAACAGCC CAACTCCAGT CTCTCGTTGG ATCTATCCCC AGCAGGACTG TCAGACTGAA     630
T  E  V  P  S  T  Y  R  S  S  G  N  S  P  T  P  V  S  R  W  I  Y  P  Q  Q  D  C  Q  T  E

GCACCCCCTC TTAGGGGGCA GGTTCCAGGA TATCCGCCTT CACAGAACCC TGGAATGACC CTGCCCCATT ATCCTTATGG AGATGGTAAT     720
A  P  P  L  R  G  Q  V  P  G  Y  P  P  S  Q  N  P  G  M  T  L  P  H  Y  P  Y  G  D  G  N

CGTAGTGTTC CACAATCAGG ACCGACTGTA CGACCACAAG AAGATGCGTG GGCTTCTCCT GGTGCTTATG GAATGGGTGG CCGTTATCCC     810
R  S  V  P  Q  S  G  P  T  V  R  P  Q  E  D  A  W  A  S  P  G  A  Y  G  M  G  G  R  Y  P
```

Fig. 16D

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TGGCCTTCAT CAGCGCCCTC AGCACCACCC GGCAATCTCT ACATGACTGA AAGTACTTCA CCATGGCCTA GCAGTGGCTC TCCCCAGTCA      900
W  P  S  S  A  P  S  A  P  P  G  N  L  Y  M  T  E  S  T  S  P  W  P  S  S  G  S  P  Q  S

CCCCCTTCAC CCCCAGTCCA GCAGCCCAAG GATTCTTCAT ACCCCTATAG CCAATCAGAT CAAAGCATGA ACCGGCACAA CTTTCCTTGC      990
P  P  S  P  P  V  Q  Q  P  K  D  S  S  Y  P  Y  S  Q  S  D  Q  S  M  N  R  H  N  F  P  C

AGTGTCCATC AGTACGAATC CTCGGGGACA GTGATCAATG AAGATTCAGA TCTTTTGGAT TCCCAAGTCC AGTATAGTGC TGAGCCTCAG     1080
S  V  H  Q  Y  E  S  S  G  T  V  I  N  E  D  S  D  L  L  D  S  Q  V  Q  Y  S  A  E  P  Q

CTGTATGGTA ATGCCACCAG TGACCATCCC AACAATCAAG ATCAAAGTAG CAGTCTTCCT GAAGAATGTG TACCTTCAGA TGAAAGTACT     1170
L  Y  G  N  A  T  S  D  H  P  N  N  Q  D  Q  S  S  S  L  P  E  E  C  V  P  S  D  E  S  T

CCTCCGAGTA TTAAAAAAAT CATACATGTG CTGGAGAAGG TCCAGTATCT TGAACAAGAA GTAGAAGAAT TTGTAGGAAA AAAGACAGAC     1260
P  P  S  I  K  K  I  I  H  V  L  E  K  V  Q  Y  L  E  Q  E  V  E  E  F  V  G  K  K  T  D

AAAGCATACT GGCTTCTGGA AGAAATGCTA ACCAAGGAAC TTTTGGAACT GGATTCAGTT GAAACTGGGG GCCAGGACTC TGTACGGCAG     1350
K  A  Y  W  L  L  E  E  M  L  T  K  E  L  L  E  L  D  S  V  E  T  G  G  Q  D  S  V  R  Q

GCCAGAAAAG AGGCTGTTTG TAAGATTCAG GCCATACTGG AAAAATTAGA AAAAAAAGGA TTATGAAAGG ATTTAGAACA AAGTGGAAGC     1440
A  R  K  E  A  V  C  K  I  Q  A  I  L  E  K  L  E  K  K  G  L

CTGTTACTAA CTTGACCAAA GAACACTTGA TTAGGTTAAT TACCCTCTTT TTGAAATGCC TGTTGATGAC AAGAAGCAAT ACATTCCAGC     1530
TTTTCCTTTG ATTTTATACT TGAAAAACTG GCAAAGGAAT GGAAGAATAT TTTAGTCATG AAGTTGTTTT CAGTTTTCAG ACGAATGAATG     1620
TAATAGGAAA CTATGGAGTT ACCAATATTG CCAAGTAGAC TCACTCCTTA AAAAATTTAT GGATATCTAC AAGCTGCTTA TTACCAGCAG     1710
GAGGGAAACA CACTTCACAC AACAGGCTTA TCAGAAACCT ACCAGATGAA ACTGGATATA ATTTGAGACA AACAGGATGT GTTTTTTTAA     1800
ACATCTGGAT ATCTTGTCAC ATTTTTGTAC ATTGTGACTG CTTTCAACAT ATACTTCATG TGTAATTATA GCTTAGACTT TAGCCTTCTT     1890
GGACTTCTGT TTTGTTTTGT TATTTGCAGT TTACAAATAT AGTATTATTC TCTAAAAAAA AAAAAAAAAA AAAAA                      1980
```

Fig.16E

FIG. 17A

CCCCCCCCCC CCCCCCCCCC CCNGAAGACG CCCGGAGCGG CTGCTGCAGC 50
CAGTAGCGGC CCCTTCACCG GCTGCCCCGC TCAGACCTAG TCGGGAGGGG 100
TGCGAGGCAT GCAGCTGGGG GCCCAGCTCC GGTGCCGCAC CCCGTAAAGG 150
GCTGATCTTC CACCTCGCCA CCTCAGCCAC GGGACGGCCAA GACCGCATCC 200
AATTCAGACT TCTTTTGGTG CTTGTGAAAC TGAACACAAC AAAAGTATGG 250
ATATGGGAAA CCAACATCCT TCTATTAGTA GGCTTCAGGA AATCCAAAAG 300
GAAGTAAAAA GTGTAGAACA GCAAGTTATC GGCTTCAGTG GTCTGTCAGA 350
TGACAAGAAT TACAAGAAAC TGGAGAGAGGAT TCTAACAAAA CAGCTTTTTG 400
AAATAGACTC TGTAGATACT GAAGGAAAAG GAGATATTCA GCAAGCTAGG 450
AAGCGGGCAG CACAGGAGAC AGAACGTCTT CTCAAAGAGT TGGAGCAGAA 500
TGCAAACCAC CCACACCGGA TTGAAATACA GAACATTTTT GAGGAAGCCC 550
AGTCCCTCGT GAGAGAGAAA ATTGTGCCAT TTTATAATGG AGGCAACTGC 600
GTAACTGATG AGTTTGAAGA AGGCATCCAA GATATCATTC TGAGGCTGAC 650
ACATGTTAAA ACTGGAGGAA AAATCTCCTT GCGGAAAGCA AGGTATCACA 700
CTTTAACCAA AATCTGTGCG GTGCAAGAGA TAATCGAAGA CTGCATGAAA 750
AAGCAGCCTT CCCTGCCGCT TTCCGAGGAT GCACATCCTT CCGTTGCCAA 800
AATCAACTTC GTGATGTGTG AGGTGAACAA GGCCCGAGGG GTCCTGATTG 850
CACTTCTGAT GGGTGTGAAC AACAATGAGA CCTGCAGGCA CTTATCCTGT 900
GTGCTCTCGG GGCTGATCGC TGACCTGGAT GCTCTAGATG TGTGCGGCCG 950
GACAGAAATC AGAAATTATC GGAGGGAGGT AGTAGAAGAT ATCAACAAAT 1000
TATTGAAATA TCTGGATTTG GAAGAGGAAG CAGACACAAC TAAAGCATTT 1050
GACCTGAGAC AGAATCATTC CATTTTAAAA ATAGAAAAGG TCCTCAAGAG 1100
AATGAGAGAA ATAAAAAATG AACTTCTCCA AGCACAAAAC CCTTCTGAAT 1150
TGTACCTGAG CTCCAAAACA GAATTGCAGG GTTTAATTGG ACAGTTGGAT 1200
GAGGTAAGTC TTGAAAAAAA CCCCTGCATC CGGGAAGCCA GGAGAAGAGC 1250
AGTGATCGAG GTGCAAACTC TGATCACATA TATTGACTTG AAGGAGGCCC 1300

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FIG. 17B

```
TTGAGAAAAG AAAGCTGTTT GCTTGTGAGG AGCACCCATC CCATAAAGCC 1350
GTCTGGAACG TCCTTGGAAA CTTGTCTGAG ATCCAGGGAG AAGTTCTTTC 1400
ATTTGATGGA AATCGAACCG ATAAGAACTA CATCCGGCTG GAAGAGCTGC 1450
TCACCAAGCA GCTGCTAGCC CTGGATGCTG TTGATCCGCA GGGAGAAGAG 1500
AAGTGTAAGG CTGCCAGGAA ACAAGCTGTG AGGCTTGCGC AGAATATTCT 1550
CAGCTATCTC GACCTGAAAT CTGATGAATG GGAGTACTGA AATACCAGAG 1600
ATCTCACTTT TGATACTGTT TTGCACTTCA TATGTGCTTC TATGTATAGA 1650
GAGCTTTCAG TTCATTGATT TATACGTGCA TATTTCAGTC TCAGTATTTA 1700
TGATTGAAGC AAATTCTATT CAGTATCTGC TGCTTTTGAT GTTGCAAGAC 1750
AAATATCATT ACAGCACGTT AACTTTTCCA TTCGGATCAT TATCTGTATG 1800
ATGTGGTGTG GTTTGTTTGG TTTGTCCTTT TTTTTGCGTT TTTAATCAGA 1850
AAACAAAATA GAGGCAGCTT TTGTAGATTT TAAATGGGTT GTGCAAGCAT 1900
TAAAATGCAG GTCTTTCAGA ATCTAGAACT AGGCATAACC TTACATAATA 1950
CTAGGAAAAT TATGAGAAAG GGGAAATTTT TGGTTAAATA AGAGTAAGGT 2000
TCAAACACAA GCAGTACATG TTCTGTTTCA TTATGCTCGA TAGAAGGCTT 2050
TTTTTTCACT TATAAGGCCT GATTGGTCCT ACCCAGCTTA ACGGGGTGGG 2100
GTTTTTTTGT TTGTTCAGAC AGTCTGTTCT TTTGTAAACA TTTTTAGTTG 2150
GAAAAACAGC ATCTGCATTT TCCCCATCCT CTACGTTTTA GAGAGGAATC 2200
TTGTTTTTGT GTGCAACATA AGAAAATTAT GAAAACTAAT AGCCAAAAAA 2250
CCTTTGAGAT TGCATTAAAG AGAAGGGATA AAGGACCAGC AATAATACCT 2300
TGTAAGTTGC TTTTGTTTGT AAAATCTGAG CTTATAGTTT TCCTTAGTGA 2350
GTAAATTCAT AAGGATGGGA ACATTTAAAT TAAGTTAATG GGCCTTTAAA 2400
AAAAAAAAAG GAAACACTCA TACCTGTAGT TGGAGGATGA ATACTGGAGA 2450
CGGGTTACCA ATGTCAGGTT ATACTAAAAC TAAATCAGAA AGTCTGAATG 2500
TAGCACATAA TGGTTCTCTT CTGTTGTCCA AGGCTGTAAA ATGGACAGCC 2550
TTGTCACACC TCCCCGGTGC TGTTTTACAA CGTGAGGGTA GACGCTGTCA 2600
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FIG. 17C

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GTAACCCAGA GGGACCAGGC CTTCCTAGGT TTTCTAGGCA GTCAGCTGTT  2650
AACCACTCAC TTAGTAAATG TCATAACTAC ACCTGCTCCA GGACCAATCA  2700
GTGAAACCTG CTCGGAATTA AAGGCTTCCT CTGGGTGCCT GCTGAACAAC  2750
TGAGCTCATG TCATGGGCAT GTGGTGGTTT CTCTGTTGCC TGAAAGAGCC  2800
ATTAAAGTCA GTCGTGCGTG AAGCATCTCT CTTCTAAAGG ATGTGTATTT  2850
CCATAAATGC TTTCTGAGGA TCCGGTACAA AATGATTTCC CAAAGTTCTG  2900
AAGTGCCTTG AGAACATGTG GGTCCGAGTG TTATAACAGA CTCCTCCCCC  2950
GGGTCACCTT TTGCCTGGTC ATCCTGTTAG AGTACATCTT TGGAAATCCA  3000
GGGTAATATT CTCTTTCAGA GATGCTCATT GTGTAACTCT GTGTAGGGAG  3050
ATAGTCACTT TAAACAGCTC AAAGTAGCTA GCTAAAGGAG TAGCCTTAAA  3100
TACCTAAAAG ATGACAGAAG CATAGCCCTT AACAAATCTT CAGCTTGTCT  3150
CTCAGTATTT CCCAATCATG AAAATCCCTT GCTATGTCTT TCCTACTAGA  3200
AATGTTCTAG AATCGCTGGA CGGTGGGGTC AGAGGGCAGT CGGTATTTAG  3250
GCCGTGAGCT TCCCATACTA CTGCAGGTCC AACTCCTGGC AACCGCGGGC  3300
TCAAGGCAGG TCATTGGAAT CCACGTTTTG GCCACAGTAG TTGTAGGATT  3350
GCTTTTCTGT ATCATAATTT TAGAATGCTC TTAAAATCTT GAGGAAGAGT  3400
TTTTATTTTT TATTTATTTT TGAGATGGAG TCTCTGTTGC CCAGGCTGCA  3450
GTGCAGTGGT GCCATCTCAG CTCACTGCAA CCTCCACCTC CCAGGTTCAA  3500
GCGATTCTCC TGCCTCAGCC ACCTGAGTAG CTGGGAGTAC AGGCATGTGG  3550
CACCATGCCT GGCTAATTTT TGTATTTTTA ATAGAGTTGA GATTTCACCA  3600
TGATGGTCAG GCTGGTCTCG AACTCCTGAC CTCGTGATCC GCCCGCCTCG  3650
GCCCCCCAAA GTGCTGGGAT TAACGGGTGT GAGCCACCGG GCCCAGCCCA  3700
GGAAGAGTTT TTAAATTAGA GCTCTGTTTA ATTATACCAC TGGGAAATCA  3750
TGGTTACGCT TCAGGCATAT TCTTCCCCAG AGTACTACTT ACATTTTAAA  3800
TTTCATTTTG TAAAGTTAAA TGTCAGCATT CCCTTTAAAA GTGTCCATTG  3850
TTCTTTGAAA GTAGACGTTT CAGTCATTCT TTTCAAACAA GTGTTTGTGT  3900
```


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FIG. 17D

ACCTTTTGCC AAGCTGTGGG CATCGTGTGT GAGTACAGGG TGCTCAGCTC 3950
TTCCACCGTC ATTTTGAATT GTTCACATGG GTAATTGGTC ATGGAAATGA 4000
TCAGATTGAC CTTGATTGAC TGTCAGGCAT GGCTTTGTTT CTAGTTTCAA 4050
TCTGTTCTCG TTCCTTGTAC CGGATTATTC TACTCCTGCA ATGAACCCTG 4100
TTGACACCGG ATTTAGCTCT TGTCGGCCTT CGTGGGGAGC TGTTTGTGTT 4150
AATATGAGCT ACTGCATGTA ATTCTTAAAC TGGGCTTGTC ACATTGTATT 4200
GTATTTTTGT GATCTGTAAT GAAAAGAATC TGTACTGCAA GTAAAACCTA 4250
CTCCCCAAAA ATGTGTGGCT TTGGGTCTGC ATTAAACGCT GTAGTCCATG 4300
TTCATGCC 4308

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FIG. 17E

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MDMGNQHPSI SRLQEIQKEV KSVEQQVIGF SGLSDDKNYK KLERILTKQL     50
FEIDSVDTEG KGDIQQARKR AAQETERLLK ELEQNANHPH RIEIQNIFEE    100
AQSLVREKIV PFYNGGNCVT DEFEEGIQDI ILRLTHVKTG GKISLRKARY    150
HTLTKICAVQ EIIEDCMKKQ PSLPLSEDAH PSVAKINFVM CEVNKARGVL    200
IALLMGVNNN ETCRHLSCVL SGLIADLDAL DVCGRTEIRN YRREVVEDIN    250
KLLKYLDLEE EADTTKAFDL RQNHSILKIE KVLKRMREIK NELLQAQNPS    300
ELYLSSKTEL QGLIGQLDEV SLEKNPCIRE ARRAVIEVQ TLITYIDLKE    350
ALEKRKLFAC EEHPSHKAVW NVLGNLSEIQ GEVLSFDGNR TDKNYIRLEE    400
LLTKQLLALD AVDPQGEEKC KAARKQAVRL AQNILSYLDL KSDEWEY       447
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Fig. 17F

```
CCCCCCCCCC CCCCCCCCCC CCNGAAGACG CCCGGAGCGG CTGCTGCAGC CAGTAGCGGC CCCTTCACCG GCTGCCCCGC TCAGACCTAG     90
TCGGGAGGGG TGCGAGGCAT GCAGCTGGGG GCCCAGCTCC GGTGCCGCAC CCCGTAAAGG GCTGATCTTC CACCTCGCCA CCTCAGCCAC    180
GGGACGCCAA GACCGCATCC AATTCAGACT TCTTTTGGTG CTTGTGAAAC TGAACACAAC AAAAGTATGG ATATGGGAAA CCAACATCCT    270
                                                                    M  D  M  G  N  Q  H  P

TCTATTAGTA GGCTTCAGGA AATCCAAAAG GAAGTAAAAA GTGTAGAACA GCAAGTTATC GGCTTCAGTG GTCTGTCAGA TGACAAGAAT    360
S  I  S  R  L  Q  E  I  Q  K  E  V  K  S  V  E  Q  Q  V  I  G  F  S  G  L  S  D  D  K  N

TACAAGAAAC TGGAGAGGAT TCTAACAAAA CAGCTTTTTG AAATAGACTC TGTAGATACT GAAGGAAAAG GAGATATTCA GCAAGCTAGG    450
Y  K  K  L  E  R  I  L  T  K  Q  L  F  E  I  D  S  V  D  T  E  G  K  G  D  I  Q  Q  A  R

AAGCGGGCAG CACAGGAGAC AGAACGTCTT CTCAAAGAGT TGGAGCAGAA TGCAAACCAC CCACACCGGA TTGAAATACA GAACATTTTT    540
K  R  A  A  Q  E  T  E  R  L  L  K  E  L  E  Q  N  A  N  H  P  H  R  I  E  I  Q  N  I  F

GAGGAAGCCC AGTCCCTCGT GAGAGAGAAA ATTGTGCCAT TTTATAATGG AGGCAACTGC GTAACTGATG AGTTTGAAGA AGGCATCCAA    630
E  E  A  Q  S  L  V  R  E  K  I  V  P  F  Y  N  G  G  N  C  V  T  D  E  F  E  E  G  I  Q

GATATCATTC TGAGGCTGAC ACATGTTAAA ACTGGAGGAA AAATCTCCTT GCGGAAAGCA AGGTATCACA CTTTAACCAA AATCTGTGCG    720
D  I  I  L  R  L  T  H  V  K  T  G  G  K  I  S  L  R  K  A  R  Y  H  T  L  T  K  I  C  A

GTGCAAGAGA TAATCGAAGA CTGCATGAAA AAGCAGCCTT CCCTGCCGCT TTCCGAGGAT GCACATCCTT CCGTTGCCAA AATCAACTTC    810
V  Q  E  I  I  E  D  C  M  K  K  Q  P  S  L  P  L  S  E  D  A  H  P  S  V  A  K  I  N  F

GTGATGTGTG AGGTGAACAA GGCCCGAGGG GTCCTGATTG CACTTCTGAT GGGTGTGAAC AACAATGAGA CCTGCAGGCA CTTATCCTGT    900
V  M  C  E  V  N  K  A  R  G  V  L  I  A  L  L  M  G  V  N  N  N  E  T  C  R  H  L  S  C

GTGCTCTCGG GGCTGATCGC TGACCTGGAT GCTCTAGATG TGTGCGGCCG GACAGAAATC AGAAATTATC GGAGGGAGGT AGTAGAAGAT    990
V  L  S  G  L  I  A  D  L  D  A  L  D  V  C  G  R  T  E  I  R  N  Y  R  R  E  V  V  E  D

ATCAACAAAT TATTGAAATA TCTGGATTTG GAAGAGGAAG CAGACACAAC TAAAGCATTT GACCTGAGAC AGAATCATTC CATTTTAAAA   1080
I  N  K  L  L  K  Y  L  D  L  E  E  E  A  D  T  T  K  A  F  D  L  R  Q  N  H  S  I  L  K
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Fig. 17G

```
ATAGAAAAGG TCCTCAAGAG AATGAGAGAA ATAAAAAATG AACTTCTCCA AGCACAAAAC CCTTCTGAAT TGTACCTGAG CTCCAAAACA   1170
I  E  K  V  L  K  R  M  R  E  I  K  N  E  L  L  Q  A  Q  N  P  S  E  L  Y  L  S  S  K  T

GAATTGCAGG GTTTAATTGG ACAGTTGGAT GAGGTAAGTC TTGAAAAAAA CCCCTGCATC CGGGAAGCCA GGAGAAGAGC AGTGATCGAG   1260
E  L  Q  G  L  I  G  Q  L  D  E  V  S  L  E  K  N  P  C  I  R  E  A  R  R  R  A  V  I  E

GTGCAAACTC TGATCACATA TATTGACTTG AAGGAGGCCC TTGAGAAAAG AAAGCTGTTT GCTTGTGAGG AGCACCCATC CCATAAAGCC   1350
V  Q  T  L  I  T  Y  I  D  L  K  E  A  L  E  K  R  K  L  F  A  C  E  E  H  P  S  H  K  A

GTCTGGAACG TCCTTGGAAA CTTGTCTGAG ATCCAGGGAG AAGTTCTTTC ATTTGATGGA AATCGAACCG ATAAGAACTA CATCCGGCTG   1440
V  W  N  V  L  G  N  L  S  E  I  Q  G  E  V  L  S  F  D  G  N  R  T  D  K  N  Y  I  R  L

GAATTGCAGG GTTTAATTGG ACAGTTGGAT GAGGTAAGTC TTGAAAAAAA CCCCTGCATC CGGGAAGCCA GGAGAAGAGC AGTGATCGAG   1260
E  L  Q  G  L  I  G  Q  L  D  E  V  S  L  E  K  N  P  C  I  R  E  A  R  R  R  A  V  I  E

GTGCAAACTC TGATCACATA TATTGACTTG AAGGAGGCCC TTGAGAAAAG AAAGCTGTTT GCTTGTGAGG AGCACCCATC CCATAAAGCC   1350
V  Q  T  L  I  T  Y  I  D  L  K  E  A  L  E  K  R  K  L  F  A  C  E  E  H  P  S  H  K  A

GTCTGGAACG TCCTTGGAAA CTTGTCTGAG ATCCAGGGAG AAGTTCTTTC ATTTGATGGA AATCGAACCG ATAAGAACTA CATCCGGCTG   1440
V  W  N  V  L  G  N  L  S  E  I  Q  G  E  V  L  S  F  D  G  N  R  T  D  K  N  Y  I  R  L

GAAGAGCTGC TCACCAAGCA GCTGCTAGCC CTGGATGCTG TTGATCCGCA GGGAGAAGAG AAGTGTAAGG CTGCCAGGAA ACAAGCTGTG   1530
E  E  L  L  T  K  Q  L  L  A  L  D  A  V  D  P  Q  G  E  E  K  C  K  A  A  R  K  Q  A  V

AGGCTTGCGC AGAATATTCT CAGCTATCTC GACCTGAAAT CTGATGAATG GGAGTACTGA AATACCAGAG ATCTCACTTT TGATACTGTT   1620
R  L  A  Q  N  I  L  S  Y  L  D  L  K  S  D  E  W  E  Y

TTGCACTTCA TATGTGCTTC TATGTATAGA GAGCTTTCAG TTCATTGATT TATACGTGCA TATTTCAGTC TCAGTATTTA TGATTGAAGC   1710
AAATTCTATT CAGTATCTGC TGCTTTTGAT GTTGCAAGAC AAATATCATT ACAGCACGTT AACTTTTCCA TTCGGATCAT TATCTGTATG   1800
ATGTGGTGTG GTTTGTTTGG TTTGTCCTTT TTTTTGCGTT TTTAATCAGA AAACAAAATA GAGGCAGCTT TTGTAGATTT TAAATGGGTT   1890
GTGCAAGCAT TAAAATGCAG GTCTTTCAGA ATCTAGAACT AGGCATAACC TTACATAATA CTAGGAAAAT TATGAGAAAG GGGAAATTTT   1980
TGGTTAAATA AGAGTAAGGT TCAAACACAA GCAGTACATG TTCTGTTTCA TTATGCTCGA TAGAAGGCTT TTTTTTCACT TATAAGGCCT   2070
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Fig. 17H

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GATTGGTCCT ACCCAGCTTA ACGGGGTGGG GTTTTTTTGT TTGTTCAGAC AGTCTGTTCT TTTGTAAACA TTTTTAGTTG GAAAAACAGC   2160
ATCTGCATTT TCCCCATCCT CTACGTTTTA GAGAGGAATC TTGTTTTTGT GTGCAACATA AGAAAATTAT GAAAACTAAT AGCCAAAAAA   2250
CCTTTGAGAT TGCATTAAAG AGAAGGGATA AAGGACCAGC AATAATACCT TGTAAGTTGC TTTTGTTTGT AAAATCTGAG CTTATAGTTT   2340
TCCTTAGTGA GTAAATTCAT AAGGATGGGA ACATTTAAAT TAAGTTAATG GGCCTTTAAA AAAAAAAAAG GAAACACTCA TACCTGTAGT   2430
TGGAGGATGA ATACTGGAGA CGGGTTACCA ATGTCAGGTT ATACTAAAAC TAAATCAGAA AGTCTGAATG TAGCACATAA TGGTTCTCTT   2520
CTGTTGTCCA AGGCTGTAAA ATGGACAGCC TTGTCACACC TCCCCGGTGC TGTTTTACAA CGTGAGGGTA GACGCTGTCA GTAACCCAGA   2610
GGGACCAGGC CTTCCTAGGT TTTCTAGGCA CTCAGCTGTT AACCACTCAC TTAGTAAATG TCATAACTAC ACCTGCTCCA GGACCAATCA   2700
GTGAAACCTG CTCGGAATTA AAGGCTTCCT CTGGGTGCCT GCTGAACAAC TGAGCTCATG TCATGGGCAT GTGGTGGTTT CTCTGTTGCC   2790
TGAAAGAGCC ATTAAAGTCA GTCGTGCGTG AAGCATCTCT CTTCTAAAGG ATGTGTATTT CCATAAATGC TTTCTGAGGA TCCGGTACAA   2880
AATGATTTCC CAAAGTTCTG AAGTGCCTTG AGAACATGTG GGTCCGAGTG TTATAACAGA CTCCTCCCCC GGGTCACCTT TTGCCTGGTC   2970
ATCCTGTTAG AGTACATCTT TGGAAATCCA GGGTAATATT CTCTTTCAGA GATGCTCATT GTGTAACTCT GTGTAGGGAG ATAGTCACTT   3060
TAAACAGCTC AAAGTAGCTA GCTAAAGGAG TAGCCTTAAA TACCTAAAAG ATGACAGAAG CATAGCCCTT AACAAATCTT CAGCTTGTCT   3150
CTCAGTATTT CCCAATCATG AAAATCCCTT GCTATGTCTT TCCTACTAGA AATGTTCTAG AATCGCTGGA CGGTGGGGTC AGAGGGCAGT   3240
CGGTATTTAG GCCGTGAGCT TCCCATACTA CTGCAGGTCC AACTCCTGGC AACCGCGGGC TCAAGGCAGG TCATTGGAAT CCACGTTTTG   3330
GCCACAGTAG TTGTAGGATT GCTTTTCTGT ATCATAATTT TAGAATGCTC TTAAAATCTT GAGGAAGAGT TTTTATTTTT TATTTATTTT   3420
TGAGATGGAG TCTCTGTTGC CCAGGCTGCA GTGCAGTGGT GCCATCTCAG CTCACTGCAA CCTCCACCTC CCAGGTTCAA GCGATTCTCC   3510
TGCCTCAGCC ACCTGAGTAG CTGGGAGTAC AGGCATGTGG CACCATGCCT GGCTAATTTT TGTATTTTTA ATAGAGTTGA GATTTCACCA   3600
TGATGGTCAG GCTGGTCTCG AACTCCTGAC CTCGTGATCC GCCCGCCTCG GCCCCCCAAA GTGCTGGGAT TAACGGGTGT GAGCCACGGC   3690
GCCCAGCCCA GGAAGAGTTT TTAAATTAGA GCTCTGTTTA ATTATACCAC TGGGAAATCA TGGTTACGCT TCAGGCATAT TCTTCCCCAG   3780
AGTACTACTT ACATTTTAAA TTTCATTTTG TAAAGTTAAA TGTCAGCATT CCCTTTAAAA GTGTCCATTG TTCTTTGAAA GTAGACGTTT   3870
CAGTCATTCT TTTCAAACAA GTGTTTGTGT ACCTTTTGCC AAGCTGTGGG CATCGTGTGT GAGTACAGGG TGCTCAGCTC TTCCACCGTC   3960
ATTTTGAATT GTTCACATGG GTAATTGGTC ATGGAAATGA TCAGATTGAC CTTGATTGAC TGTCAGGCAT GGCTTTGTTT CTAGTTTCAA   4050
TCTGTTCTCG TTCCTTGTAC CGGATTATTC TACTCCTGCA ATGAACCCTG TTGACACCGG ATTTAGCTCT TGTCGGCCTT CGTGGGGAGC   4140
TGTTTGTGTT AATATGAGCT ACTGCATGTA ATTCTTAAAC TGGGCTTGTC ACATTGTATT GTATTTTTGT GATCTGTAAT GAAAAGAATC   4230
TGTACTGCAA GTAAAACCTA CTCCCCAAAA ATGTGTGGCT TTGGGTCTGC ATTAAACGCT GTAGTCCATG TTCATGCC               4320
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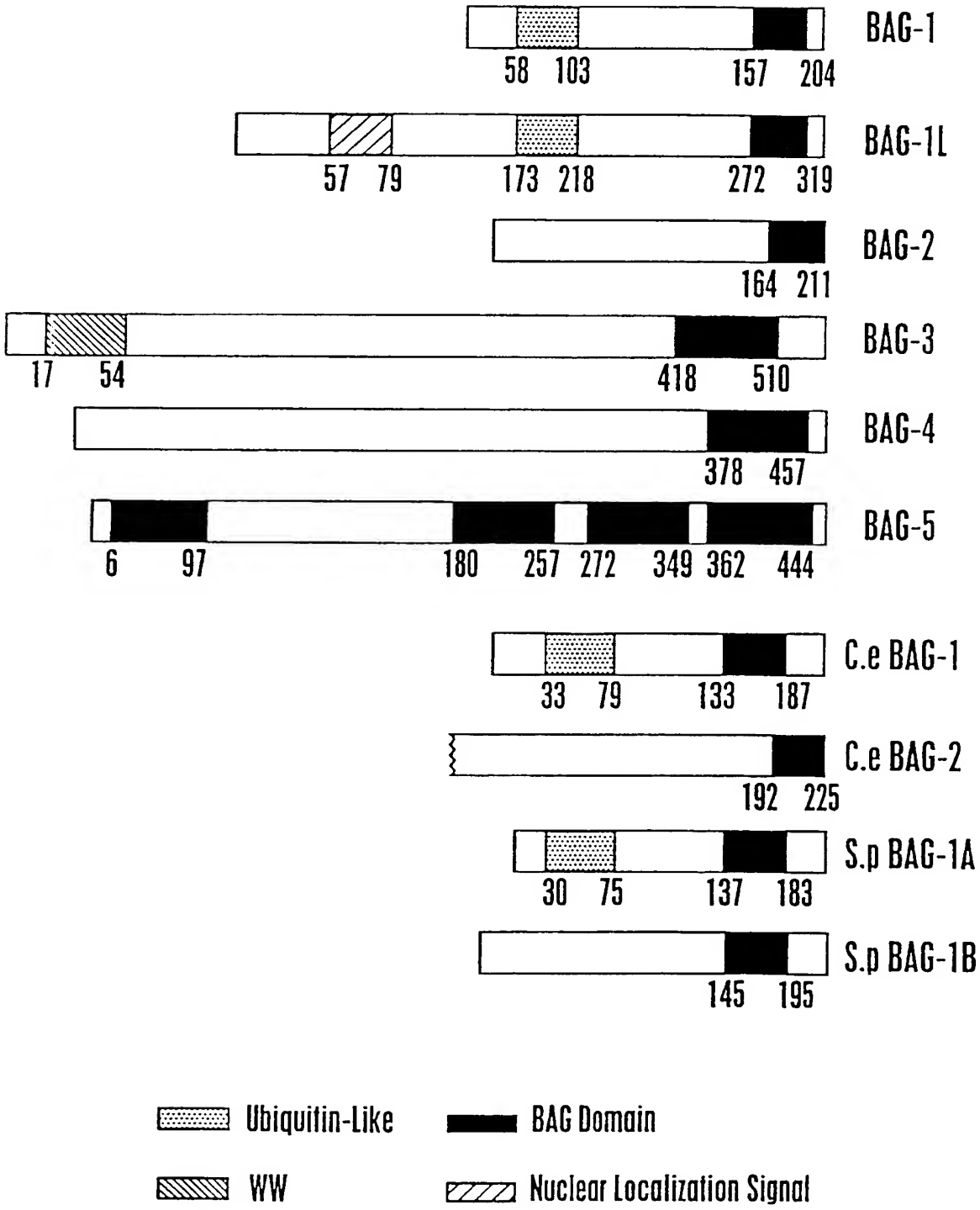
Fig. 18



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SEQUENCE LISTING

<110> Reed, John C.
Takayama, Shinichi
The Burnham Institute

<120> Novel BAG Proteins and Nucleic Acid Molecules Encoding Them

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Gly Gly Ala Arg Arg Pro Arg Gly Asp Arg Glu Arg Leu Gly Ser Arg
5 10 15 20

ctg cgc gcc ctt cgg cca ggc cgg gag ccg cgc cag tcg gag ccc ccg 153
Leu Arg Ala Leu Arg Pro Gly Arg Glu Pro Arg Gln Ser Glu Pro Pro
25 30 35

gcc cag cgt ggt ccg cct ccc tct cgg cgt cca cct gcc cgg agt act 201
Ala Gln Arg Gly Pro Pro Pro Ser Arg Arg Pro Pro Ala Arg Ser Thr
40 45 50

gcc agc ggg cat gac cga ccc acc agg ggc gcc gcc gcc ggc gct cgc 249

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          55                  60                  65

agg ccg cgg atg aag aag aaa acc cgg cgc cgc tcg acc cgg agc gag   297
Arg Pro Arg Met Lys Lys Lys Thr Arg Arg Arg Ser Thr Arg Ser Glu
     70                  75                  80

gag ttg acc cgg agc gag gag ttg acc ctg agt gag gaa gcg acc tgg   345
Glu Leu Thr Arg Ser Glu Glu Leu Thr Leu Ser Glu Glu Ala Thr Trp
 85                  90                  95                 100

agt gaa gag gcg acc cag agt gag gag gcg acc cag ggc gaa gag atg   393
Ser Glu Glu Ala Thr Gln Ser Glu Glu Ala Thr Gln Gly Glu Glu Met
                105                 110                 115

aat cgg agc cag gag gtg acc cgg gac gag gag tcg acc cgg agc gag   441
Asn Arg Ser Gln Glu Val Thr Arg Asp Glu Glu Ser Thr Arg Ser Glu
            120                 125                 130

gag gtg acc agg gag gaa atg gcg gca gct ggg ctc acc gtg act gtc   489
Glu Val Thr Arg Glu Glu Met Ala Ala Ala Gly Leu Thr Val Thr Val
        135                 140                 145

acc cac agc aat gag aag cac gac ctt cat gtt acc tcc cag cag ggc   537
Thr His Ser Asn Glu Lys His Asp Leu His Val Thr Ser Gln Gln Gly
    150                 155                 160

agc agt gaa cca gtt gtc caa gac ctg gcc cag gtt gtt gaa gag gtc   585
Ser Ser Glu Pro Val Val Gln Asp Leu Ala Gln Val Val Glu Glu Val
165                 170                 175                 180

ata ggg gtt cca cag tct ttt cag aaa ctc ata ttt aag gga aaa tct   633
Ile Gly Val Pro Gln Ser Phe Gln Lys Leu Ile Phe Lys Gly Lys Ser
                185                 190                 195

ctg aag gaa atg gaa aca ccg ttg tca gca ctt gga ata caa gat ggt   681
Leu Lys Glu Met Glu Thr Pro Leu Ser Ala Leu Gly Ile Gln Asp Gly
            200                 205                 210

tgc cgg gtc atg tta att ggg aaa aag aac agt cca cag gaa gag gtt   729
Cys Arg Val Met Leu Ile Gly Lys Lys Asn Ser Pro Gln Glu Glu Val
        215                 220                 225

gaa cta aag aag ttg aaa cat ttg gag aag tct gtg gag aag ata gct   777
Glu Leu Lys Lys Leu Lys His Leu Glu Lys Ser Val Glu Lys Ile Ala
    230                 235                 240

gac cag ctg gaa gag ttg aat aaa gag ctt act gga atc cag cag ggt   825
```


BNSDOCID <WO 0014106A1 IA>

```
Asp Gln Leu Glu Glu Leu Asn Lys Glu Leu Thr Gly Ile Gln Gln Gly
245                 250                 255                 260

ttt ctg ccc aag gat ttg caa gct gaa gct ctc tgc aaa ctt gat agg    873
Phe Leu Pro Lys Asp Leu Gln Ala Glu Ala Leu Cys Lys Leu Asp Arg
                265                 270                 275

aga gta aaa gcc aca ata gag cag ttt atg aag atc ttg gag gag att    921
Arg Val Lys Ala Thr Ile Glu Gln Phe Met Lys Ile Leu Glu Glu Ile
            280                 285                 290

gac aca ctg atc ctg cca gaa aat ttc aaa gac agt aga ttg aaa agg    969
Asp Thr Leu Ile Leu Pro Glu Asn Phe Lys Asp Ser Arg Leu Lys Arg
        295                 300                 305

aaa ggc ttg gta aaa aag gtt cag gca ttc cta gcc gag tgt gac aca   1017
Lys Gly Leu Val Lys Lys Val Gln Ala Phe Leu Ala Glu Cys Asp Thr
    310                 315                 320

gtg gag cag aac atc tgc cag gag act gag cgg ctg cag tct aca aac   1065
Val Glu Gln Asn Ile Cys Gln Glu Thr Glu Arg Leu Gln Ser Thr Asn
325                 330                 335                 340

ttt gcc ctg gcc gag tgaggtgtag cagaaaaagg ctgtgctgcc ctgaagaatg   1120
Phe Ala Leu Ala Glu
                345

gcgccaccag ctctgccgtc tctggatcgg aatttacctg atttcttcag ggctgctggg 1180

ggcaactggc catttgccaa ttttcctact ctcacactgg ttctcaatga aaaatagtgt 1240

ctttgtgatt tgagtaaagc tcctattctg tttttcacaa aaaaaaaaaa a           1291
```

<210> 2
<211> 345
<212> PRT
<213> Homo sapiens

<400> 2

```
Leu Ala Gln Arg Gly Gly Ala Arg Arg Pro Arg Gly Asp Arg Glu Arg
  1               5                  10                  15

Leu Gly Ser Arg Leu Arg Ala Leu Arg Pro Gly Arg Glu Pro Arg Gln
            20                  25                  30

Ser Glu Pro Pro Ala Gln Arg Gly Pro Pro Pro Ser Arg Arg Pro Pro
        35                  40                  45
```


BNSDOCID <WO 0014106A1 IA>

```
Ala Arg Ser Thr Ala Ser Gly His Asp Arg Pro Thr Arg Gly Ala Ala
     50                  55                  60

Ala Gly Ala Arg Arg Pro Arg Met Lys Lys Lys Thr Arg Arg Arg Ser
 65                  70                  75                  80

Thr Arg Ser Glu Glu Leu Thr Arg Ser Glu Glu Leu Thr Leu Ser Glu
                 85                  90                  95

Glu Ala Thr Trp Ser Glu Glu Ala Thr Gln Ser Glu Glu Ala Thr Gln
            100                 105                 110

Gly Glu Glu Met Asn Arg Ser Gln Glu Val Thr Arg Asp Glu Glu Ser
        115                 120                 125

Thr Arg Ser Glu Glu Val Thr Arg Glu Glu Met Ala Ala Ala Gly Leu
    130                 135                 140

Thr Val Thr Val Thr His Ser Asn Glu Lys His Asp Leu His Val Thr
145                 150                 155                 160

Ser Gln Gln Gly Ser Ser Glu Pro Val Val Gln Asp Leu Ala Gln Val
                165                 170                 175

Val Glu Glu Val Ile Gly Val Pro Gln Ser Phe Gln Lys Leu Ile Phe
            180                 185                 190

Lys Gly Lys Ser Leu Lys Glu Met Glu Thr Pro Leu Ser Ala Leu Gly
        195                 200                 205

Ile Gln Asp Gly Cys Arg Val Met Leu Ile Gly Lys Lys Asn Ser Pro
    210                 215                 220

Gln Glu Glu Val Glu Leu Lys Lys Leu Lys His Leu Glu Lys Ser Val
225                 230                 235                 240

Glu Lys Ile Ala Asp Gln Leu Glu Glu Leu Asn Lys Glu Leu Thr Gly
                245                 250                 255

Ile Gln Gln Gly Phe Leu Pro Lys Asp Leu Gln Ala Glu Ala Leu Cys
            260                 265                 270

Lys Leu Asp Arg Arg Val Lys Ala Thr Ile Glu Gln Phe Met Lys Ile
        275                 280                 285

Leu Glu Glu Ile Asp Thr Leu Ile Leu Pro Glu Asn Phe Lys Asp Ser
    290                 295                 300
```


BNSDOCID <WO_0014106A1_A>

```
Arg Leu Lys Arg Lys Gly Leu Val Lys Lys Val Gln Ala Phe Leu Ala
305                 310                 315                 320

Glu Cys Asp Thr Val Glu Gln Asn Ile Cys Gln Glu Thr Glu Arg Leu
                325                 330                 335

Gln Ser Thr Asn Phe Ala Leu Ala Glu
            340                 345
```

<210> 3
<211> 1179
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (160)..(792)

<400> 3

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gcagccgcgg tgtcgcgaag tcctcccggg ttgcccccgc ggcgtcagag ggagggcggg 60

cgccgcgttg gtgacggcga ccctgcagcc caaggagcgc tccactcgct gccgccggag 120

ggccggtgac ctcttggcta ccccgcgtcg gaggcttag atg gct cag gcg aag    174
                                        Met Ala Gln Ala Lys
                                          1               5

atc aac gct aaa gcc aac gag ggg cgc ttc tgc cgc tcc tcc tcc atg   222
Ile Asn Ala Lys Ala Asn Glu Gly Arg Phe Cys Arg Ser Ser Ser Met
                10                  15                  20

gct gac cgc tcc agc cgc ctg ctg gag agc ctg gac cag ctg gag ctc   270
Ala Asp Arg Ser Ser Arg Leu Leu Glu Ser Leu Asp Gln Leu Glu Leu
            25                  30                  35

agg gtt gaa gct ttg aga gaa gca gca act gct gtt gag caa gag aaa   318
Arg Val Glu Ala Leu Arg Glu Ala Ala Thr Ala Val Glu Gln Glu Lys
        40                  45                  50

gaa atc ctt ctg gaa atg atc cac agt atc caa aat agc cag gac atg   366
Glu Ile Leu Leu Glu Met Ile His Ser Ile Gln Asn Ser Gln Asp Met
    55                  60                  65

agg cag atc agt gac gga gaa aga gaa gaa tta aat ctg act gca aac   414
Arg Gln Ile Ser Asp Gly Glu Arg Glu Glu Leu Asn Leu Thr Ala Asn
70                  75                  80                  85
```


BNSDOCID <WO 0014106A1 IA>

```
cgt ttg atg gga aga act ctc acc gtt gaa gtg tca gta gaa aca att   462
Arg Leu Met Gly Arg Thr Leu Thr Val Glu Val Ser Val Glu Thr Ile
                 90                  95                 100

aga aac ccc cag cag caa gaa tcc cta aag cat gcc aca agg att att   510
Arg Asn Pro Gln Gln Gln Glu Ser Leu Lys His Ala Thr Arg Ile Ile
            105                 110                 115

gat gag gtg gtc aat aag ttt ctg gat gat ttg gga aat gcc aag agt   558
Asp Glu Val Val Asn Lys Phe Leu Asp Asp Leu Gly Asn Ala Lys Ser
        120                 125                 130

cat tta atg tcg ctc tac agt gca tgt tca tct gag gtg cca cat ggg   606
His Leu Met Ser Leu Tyr Ser Ala Cys Ser Ser Glu Val Pro His Gly
    135                 140                 145

cca gtt gat cag aag ttt caa tcc ata gta att ggc tgt gct ctt gaa   654
Pro Val Asp Gln Lys Phe Gln Ser Ile Val Ile Gly Cys Ala Leu Glu
150                 155                 160                 165

gat cag aag aaa att aag aga aga tta gag act ctg ctt aga aat att   702
Asp Gln Lys Lys Ile Lys Arg Arg Leu Glu Thr Leu Leu Arg Asn Ile
                170                 175                 180

gaa aac tct gac aag gcc atc aag cta tta gag cat tct aaa gga gct   750
Glu Asn Ser Asp Lys Ala Ile Lys Leu Leu Glu His Ser Lys Gly Ala
            185                 190                 195

ggt tcc aaa act ctg caa caa aat gct gaa agc aga ttc aat           792
Gly Ser Lys Thr Leu Gln Gln Asn Ala Glu Ser Arg Phe Asn
        200                 205                 210

tagtcttcaa acctaagagc atttacacaa tacacaaggt gtaaaaatga taaaatacta 852

ttttaattga taactagttc tttgttaggt ataaccactt agttgacact gatagttgtt 912

tcagatgagg aaaatattcc atcaagtatc ttcagttttg tgaataacaa aactagcaat 972

attttaatta tctatctaga gatttttttag attgaattct tgtcttgtac taggatctag 1032

catatttcac tattctgtgg atgaatacat agtttgtggg gaaaacaaac gttcagctag 1092

gggcaaaaag catgactgct ttttcctgtc tggcatggaa tcacgcagtc accttgggca 1152

tttagtttac tagaaattct ttactgg                                    1179
```


BNSDOCID <WO 0014106A1 IA>

<210> 4
<211> 211
<212> PRT
<213> Homo sapiens

<400> 4

```
Met Ala Gln Ala Lys Ile Asn Ala Lys Ala Asn Glu Gly Arg Phe Cys
  1               5                  10                  15

Arg Ser Ser Ser Met Ala Asp Arg Ser Ser Arg Leu Leu Glu Ser Leu
             20                  25                  30

Asp Gln Leu Glu Leu Arg Val Glu Ala Leu Arg Glu Ala Ala Thr Ala
         35                  40                  45

Val Glu Gln Glu Lys Glu Ile Leu Leu Glu Met Ile His Ser Ile Gln
     50                  55                  60

Asn Ser Gln Asp Met Arg Gln Ile Ser Asp Gly Glu Arg Glu Glu Leu
 65                  70                  75                  80

Asn Leu Thr Ala Asn Arg Leu Met Gly Arg Thr Leu Thr Val Glu Val
                 85                  90                  95

Ser Val Glu Thr Ile Arg Asn Pro Gln Gln Gln Glu Ser Leu Lys His
            100                 105                 110

Ala Thr Arg Ile Ile Asp Glu Val Val Asn Lys Phe Leu Asp Asp Leu
        115                 120                 125

Gly Asn Ala Lys Ser His Leu Met Ser Leu Tyr Ser Ala Cys Ser Ser
    130                 135                 140

Glu Val Pro His Gly Pro Val Asp Gln Lys Phe Gln Ser Ile Val Ile
145                 150                 155                 160

Gly Cys Ala Leu Glu Asp Gln Lys Lys Ile Lys Arg Arg Leu Glu Thr
                165                 170                 175

Leu Leu Arg Asn Ile Glu Asn Ser Asp Lys Ala Ile Lys Leu Leu Glu
            180                 185                 190

His Ser Lys Gly Ala Gly Ser Lys Thr Leu Gln Gln Asn Ala Glu Ser
        195                 200                 205

Arg Phe Asn
    210
```


BNSDOCID <WO 0014106A1 IA>

<210> 5
<211> 2528
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(2031)

<400> 5

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gcg gag ctc cgc atc caa ccc cgg gcc gcg gcc aac ttc tct gga ctg   48
Ala Glu Leu Arg Ile Gln Pro Arg Ala Ala Ala Asn Phe Ser Gly Leu
  1               5                  10                  15

gac cag aag ttt cta gcc ggc cag ttg cta cct ccc ttt atc tcc tcc   96
Asp Gln Lys Phe Leu Ala Gly Gln Leu Leu Pro Pro Phe Ile Ser Ser
             20                  25                  30

ttc ccc tct ggc agc gag gag gct att tcc aga cac ttc cac ccc tct  144
Phe Pro Ser Gly Ser Glu Glu Ala Ile Ser Arg His Phe His Pro Ser
         35                  40                  45

ctg gcc acg tca ccc ccg cct tta att cat aaa ggt gcc cgg cgc cgg  192
Leu Ala Thr Ser Pro Pro Pro Leu Ile His Lys Gly Ala Arg Arg Arg
     50                  55                  60

ctt ccc gga cac gtc ggc ggc gga gag ggg ccc acg gcg gcg gcc cgg  240
Leu Pro Gly His Val Gly Gly Gly Glu Gly Pro Thr Ala Ala Ala Arg
 65                  70                  75                  80

cca gag act cgg cgc ccg gag cca gcg ccc cgc acc cgc gcc cca gcg  288
Pro Glu Thr Arg Arg Pro Glu Pro Ala Pro Arg Thr Arg Ala Pro Ala
                 85                  90                  95

ggc aga ccc caa ccc agc atg agc gcc gcc acc cac tcg ccc atg atg  336
Gly Arg Pro Gln Pro Ser Met Ser Ala Ala Thr His Ser Pro Met Met
            100                 105                 110

cag gtg gcg tcc ggc aac ggt gac cgc gac cct ttg ccc ccc gga tgg  384
Gln Val Ala Ser Gly Asn Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp
        115                 120                 125

gag atc aag atc gac ccg cag acc ggc tgg ccc ttc ttc gtg gac cac  432
Glu Ile Lys Ile Asp Pro Gln Thr Gly Trp Pro Phe Phe Val Asp His
    130                 135                 140

aac agc cgc acc act acg tgg aac gac ccg cgc gtg ccc tct gag ggc  480
```


BNSDOCID <WO_0014106A1_IA>

```
Asn Ser Arg Thr Thr Thr Trp Asn Asp Pro Arg Val Pro Ser Glu Gly
145                 150                 155                 160

ccc aag gag act cca tcc tct gcc aat ggc cct tcc cgg gag ggc tct   528
Pro Lys Glu Thr Pro Ser Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser
                165                 170                 175

agg ctg ccg cct gct agg gaa ggc cac cct gtg tac ccc cag ctc cga   576
Arg Leu Pro Pro Ala Arg Glu Gly His Pro Val Tyr Pro Gln Leu Arg
            180                 185                 190

cca ggc tac att ccc att cct gtg ctc cat gaa ggc gct gag aac cgg   624
Pro Gly Tyr Ile Pro Ile Pro Val Leu His Glu Gly Ala Glu Asn Arg
        195                 200                 205

cag gtg cac cct ttc cat gtc tat ccc cag cct ggg atg cag cga ttc   672
Gln Val His Pro Phe His Val Tyr Pro Gln Pro Gly Met Gln Arg Phe
    210                 215                 220

cga act gag gcg gca gca gcg gct cct cag agg tcc cag tca cct ctg   720
Arg Thr Glu Ala Ala Ala Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu
225                 230                 235                 240

cgg ggc atg cca gaa acc act cag cca gat aaa cag tgt gga cag gtg   768
Arg Gly Met Pro Glu Thr Thr Gln Pro Asp Lys Gln Cys Gly Gln Val
                245                 250                 255

gca gcg gcg gcg gca gcc cag ccc cca gcc tcc cac gga cct gag cgg   816
Ala Ala Ala Ala Ala Ala Gln Pro Pro Ala Ser His Gly Pro Glu Arg
            260                 265                 270

tcc cag tct cca gct gcc tct gac tgc tca tcc tca tcc tcc tcg gcc   864
Ser Gln Ser Pro Ala Ala Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala
        275                 280                 285

agc ctg cct tcc tcc ggc agg agc agc ctg ggc agt cac cag ctc ccg   912
Ser Leu Pro Ser Ser Gly Arg Ser Ser Leu Gly Ser His Gln Leu Pro
    290                 295                 300

cgg ggg tac atc tcc att ccg gtg ata cac gag cag aac gtt acc cgg   960
Arg Gly Tyr Ile Ser Ile Pro Val Ile His Glu Gln Asn Val Thr Arg
305                 310                 315                 320

cca gca gcc cag ccc tcc ttc cac aaa gcc cag aag acg cac tac cca  1008
Pro Ala Ala Gln Pro Ser Phe His Lys Ala Gln Lys Thr His Tyr Pro
                325                 330                 335

gcg cag agg ggt gag tac cag acc cac cag cct gtg tac cac aag atc  1056
```


BNSDOCID: <WO 0014106A1 IA>

```
Ala Gln Arg Gly Glu Tyr Gln Thr His Gln Pro Val Tyr His Lys Ile
            340                 345                 350

cag ggg gat gac tgg gag ccc cgg ccc ctg cgg gcg gca tcc ccg ttc   1104
Gln Gly Asp Asp Trp Glu Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe
        355                 360                 365

agg tca tct gtc cag ggt gca tcg agc cgg gag ggc tca cca gcc agg   1152
Arg Ser Ser Val Gln Gly Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg
    370                 375                 380

agc agc acg cca ctc cac tcc ccc tcg ccc atc cgt gtg cac acc gtg   1200
Ser Ser Thr Pro Leu His Ser Pro Ser Pro Ile Arg Val His Thr Val
385                 390                 395                 400

gtc gac agg cct cag cag ccc atg acc cat cga gaa act gca cct gtt   1248
Val Asp Arg Pro Gln Gln Pro Met Thr His Arg Glu Thr Ala Pro Val
                405                 410                 415

tcc cag cct gaa aac aaa cca gaa agt aag cca ggc cca gtt gga cca   1296
Ser Gln Pro Glu Asn Lys Pro Glu Ser Lys Pro Gly Pro Val Gly Pro
            420                 425                 430

gaa ctc cct cct gga cac atc cca att caa gtg atc cgc aaa gag gtg   1344
Glu Leu Pro Pro Gly His Ile Pro Ile Gln Val Ile Arg Lys Glu Val
        435                 440                 445

gat tct aaa cct gtt tcc cag aag ccc cca cct ccc tct gag aag gta   1392
Asp Ser Lys Pro Val Ser Gln Lys Pro Pro Pro Pro Ser Glu Lys Val
    450                 455                 460

gag gtg aaa gtt ccc cct gct cca gtt cct tgt cct cct ccc agc cct   1440
Glu Val Lys Val Pro Pro Ala Pro Val Pro Cys Pro Pro Pro Ser Pro
465                 470                 475                 480

ggc cct tct gct gtc ccc tct tcc ccc aag agt gtg gct aca gaa gag   1488
Gly Pro Ser Ala Val Pro Ser Ser Pro Lys Ser Val Ala Thr Glu Glu
                485                 490                 495

agg gca gcc ccc agc act gcc cct gca gaa gct aca cct cca aaa cca   1536
Arg Ala Ala Pro Ser Thr Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro
            500                 505                 510

gga gaa gcc gag gct ccc cca aaa cat cca gga gtg ctg aaa gtg gaa   1584
Gly Glu Ala Glu Ala Pro Pro Lys His Pro Gly Val Leu Lys Val Glu
        515                 520                 525

gcc atc ctg gag aag gtg cag ggg ctg gag cag gct gta gac aac ttt   1632
```


BNSDOCID <WO__0014106A1_!A>

```
Ala Ile Leu Glu Lys Val Gln Gly Leu Glu Gln Ala Val Asp Asn Phe
    530                 535                 540

gaa ggc aag aag act gac aaa aag tac ctg atg atc gaa gag tat ttg  1680
Glu Gly Lys Lys Thr Asp Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu
545                 550                 555                 560

acc aaa gag ctg ctg gcc ctg gat tca gtg gac ccc gag gga cga gcc  1728
Thr Lys Glu Leu Leu Ala Leu Asp Ser Val Asp Pro Glu Gly Arg Ala
                565                 570                 575

gat gtg cgt cag gcc agg aga gac ggt gtc agg aag gtt cag acc atc  1776
Asp Val Arg Gln Ala Arg Arg Asp Gly Val Arg Lys Val Gln Thr Ile
            580                 585                 590

ttg gaa aaa ctt gaa cag aaa gcc att gat gtc cca ggt caa gtc cag  1824
Leu Glu Lys Leu Glu Gln Lys Ala Ile Asp Val Pro Gly Gln Val Gln
        595                 600                 605

gtc tat gaa ctc cag ccc agc aac ctt gaa gca gat cag cca ctg cag  1872
Val Tyr Glu Leu Gln Pro Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln
    610                 615                 620

gca atc atg gag atg ggt gcc gtg gca gca gac aag ggc aag aaa aat  1920
Ala Ile Met Glu Met Gly Ala Val Ala Ala Asp Lys Gly Lys Lys Asn
625                 630                 635                 640

gct gga aat gca gaa gat ccc cac aca gaa acc cag cag cca gaa gcc  1968
Ala Gly Asn Ala Glu Asp Pro His Thr Glu Thr Gln Gln Pro Glu Ala
                645                 650                 655

aca gca gca gcg act tca aac ccc agc agc atg aca gac acc cct ggt  2016
Thr Ala Ala Ala Thr Ser Asn Pro Ser Ser Met Thr Asp Thr Pro Gly
            660                 665                 670

aac cca gca gca ccg tagcctctgc cctgtaaaag tcagactcgg aaccgatgtg  2071
Asn Pro Ala Ala Pro
        675

tgctttaggg attttagttg catgcatttc agagacttta ggtcagttgg ttttgattag 2131

ctgcttggta tgcagtactt gggtgaggca aacactataa agggctaaaa gggaaaatga 2191

tgcttttctt caatattctt actcttgtac aattaangaa gttgcttgtt gtttgagaag 2251

tttaaccccg ttgcttgttc tgcagccctg tcnacttggg caccccccacc acctgttagc 2311

tgtggttgtg cactgtcttt tgtagctctg gactggaggg gtagatgggg agtcaattac 2371
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BNSDOCID <WO 0014106A1 IA>

ccatcacata aatatgaaac atttatcaga aatgttgcca ttttaatgag atgattttct 2431

tcatctcata attaaaatac ctgactttag agagagtaaa atgtgccagg agccatagga 2491

atatctgtat gttggatgac tttaatgcta catttth 2528

<210> 6
<211> 677
<212> PRT
<213> Homo sapiens

<400> 6

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Ala Glu Leu Arg Ile Gln Pro Arg Ala Ala Ala Asn Phe Ser Gly Leu
  1               5                  10                  15

Asp Gln Lys Phe Leu Ala Gly Gln Leu Leu Pro Pro Phe Ile Ser Ser
             20                  25                  30

Phe Pro Ser Gly Ser Glu Glu Ala Ile Ser Arg His Phe His Pro Ser
         35                  40                  45

Leu Ala Thr Ser Pro Pro Pro Leu Ile His Lys Gly Ala Arg Arg Arg
     50                  55                  60

Leu Pro Gly His Val Gly Gly Gly Glu Gly Pro Thr Ala Ala Ala Arg
 65                  70                  75                  80

Pro Glu Thr Arg Arg Pro Glu Pro Ala Pro Arg Thr Arg Ala Pro Ala
                 85                  90                  95

Gly Arg Pro Gln Pro Ser Met Ser Ala Ala Thr His Ser Pro Met Met
            100                 105                 110

Gln Val Ala Ser Gly Asn Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp
        115                 120                 125

Glu Ile Lys Ile Asp Pro Gln Thr Gly Trp Pro Phe Phe Val Asp His
    130                 135                 140

Asn Ser Arg Thr Thr Thr Trp Asn Asp Pro Arg Val Pro Ser Glu Gly
145                 150                 155                 160

Pro Lys Glu Thr Pro Ser Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser
                165                 170                 175

Arg Leu Pro Pro Ala Arg Glu Gly His Pro Val Tyr Pro Gln Leu Arg
```


BNSDOCID <WO 0014106A1 I_A>

180 185 190

Pro Gly Tyr Ile Pro Ile Pro Val Leu His Glu Gly Ala Glu Asn Arg
195 200 205

Gln Val His Pro Phe His Val Tyr Pro Gln Pro Gly Met Gln Arg Phe
210 215 220

Arg Thr Glu Ala Ala Ala Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu
225 230 235 240

Arg Gly Met Pro Glu Thr Thr Gln Pro Asp Lys Gln Cys Gly Gln Val
245 250 255

Ala Ala Ala Ala Ala Ala Gln Pro Pro Ala Ser His Gly Pro Glu Arg
260 265 270

Ser Gln Ser Pro Ala Ala Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala
275 280 285

Ser Leu Pro Ser Ser Gly Arg Ser Ser Leu Gly Ser His Gln Leu Pro
290 295 300

Arg Gly Tyr Ile Ser Ile Pro Val Ile His Glu Gln Asn Val Thr Arg
305 310 315 320

Pro Ala Ala Gln Pro Ser Phe His Lys Ala Gln Lys Thr His Tyr Pro
325 330 335

Ala Gln Arg Gly Glu Tyr Gln Thr His Gln Pro Val Tyr His Lys Ile
340 345 350

Gln Gly Asp Asp Trp Glu Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe
355 360 365

Arg Ser Ser Val Gln Gly Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg
370 375 380

Ser Ser Thr Pro Leu His Ser Pro Ser Pro Ile Arg Val His Thr Val
385 390 395 400

Val Asp Arg Pro Gln Gln Pro Met Thr His Arg Glu Thr Ala Pro Val
405 410 415

Ser Gln Pro Glu Asn Lys Pro Glu Ser Lys Pro Gly Pro Val Gly Pro
420 425 430

Glu Leu Pro Pro Gly His Ile Pro Ile Gln Val Ile Arg Lys Glu Val

BNSDOCID <WO 0014106A1 IA>

435 440 445

Asp Ser Lys Pro Val Ser Gln Lys Pro Pro Pro Pro Ser Glu Lys Val
450 455 460

Glu Val Lys Val Pro Pro Ala Pro Val Pro Cys Pro Pro Pro Ser Pro
465 470 475 480

Gly Pro Ser Ala Val Pro Ser Ser Pro Lys Ser Val Ala Thr Glu Glu
485 490 495

Arg Ala Ala Pro Ser Thr Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro
500 505 510

Gly Glu Ala Glu Ala Pro Pro Lys His Pro Gly Val Leu Lys Val Glu
515 520 525

Ala Ile Leu Glu Lys Val Gln Gly Leu Glu Gln Ala Val Asp Asn Phe
530 535 540

Glu Gly Lys Lys Thr Asp Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu
545 550 555 560

Thr Lys Glu Leu Leu Ala Leu Asp Ser Val Asp Pro Glu Gly Arg Ala
565 570 575

Asp Val Arg Gln Ala Arg Arg Asp Gly Val Arg Lys Val Gln Thr Ile
580 585 590

Leu Glu Lys Leu Glu Gln Lys Ala Ile Asp Val Pro Gly Gln Val Gln
595 600 605

Val Tyr Glu Leu Gln Pro Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln
610 615 620

Ala Ile Met Glu Met Gly Ala Val Ala Ala Asp Lys Gly Lys Lys Asn
625 630 635 640

Ala Gly Asn Ala Glu Asp Pro His Thr Glu Thr Gln Gln Pro Glu Ala
645 650 655

Thr Ala Ala Ala Thr Ser Asn Pro Ser Ser Met Thr Asp Thr Pro Gly
660 665 670

Asn Pro Ala Ala Pro
675

SNSDOCID <WO 0014106A1 A>

<210> 7
<211> 1010
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (323)..(1009)

<400> 7
acgatatcct gtaagaccaa gaattgcaag gccagagttt gaattcttat acaaatggag 60

cgtatggtcc aacatacccc ccaggccctg gggcaaatac tgcctcatac tcaggggctt 120

attatgcacc tggttatact cagaccagtt actccacaga agttccaagt acttaccgtt 180

catctggcaa cagcccaact ccagtctctc gttggatcta tccccagcag gactgtcaag 240

actgaagcac cccctcttaa ggggcaggtt ccaggatatc cgccttcaca gaaccctgga 300

atgaccctgc cccattatcc tt atg gag atg gta atc gta gtg ttc cac aat 352
Met Glu Met Val Ile Val Val Phe His Asn
1 5 10

cac ggc cga ctg tac gac cac aag aaa gat gcg tgg gct tct cct ggt 400
His Gly Arg Leu Tyr Asp His Lys Lys Asp Ala Trp Ala Ser Pro Gly
15 20 25

gct tat gga atg ggt ggc cgt tat ccc tgg cct tca tca gcg ccc tca 448
Ala Tyr Gly Met Gly Gly Arg Tyr Pro Trp Pro Ser Ser Ala Pro Ser
30 35 40

gca cca ccc ggc aat ctc tac atg act gaa agt act tca cca tgg cct 496
Ala Pro Pro Gly Asn Leu Tyr Met Thr Glu Ser Thr Ser Pro Trp Pro
45 50 55

agc agt ggc tct ccc cag tca ccc cct tca ccc cca gtc cag cag ccc 544
Ser Ser Gly Ser Pro Gln Ser Pro Pro Ser Pro Pro Val Gln Gln Pro
60 65 70

aag gat tct tca tac ccc tat agc caa tca gat caa agc atg aac cgg 592
Lys Asp Ser Ser Tyr Pro Tyr Ser Gln Ser Asp Gln Ser Met Asn Arg
75 80 85 90

cac aac ttt cct tgc agt gtc cat cag tac gaa tcc tcg ggg aca gtg 640
His Asn Phe Pro Cys Ser Val His Gln Tyr Glu Ser Ser Gly Thr Val
95 100 105

BNSDOCID <WO 0014106A1 IA>

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aac aat gat gat tca gat ctt ttg gat tcc caa gtc cag tat agt gct   688
Asn Asn Asp Asp Ser Asp Leu Leu Asp Ser Gln Val Gln Tyr Ser Ala
            110                 115                 120

gag cct cag ctg tat ggt aat gcc acc agt gac cat ccc aac aat caa   736
Glu Pro Gln Leu Tyr Gly Asn Ala Thr Ser Asp His Pro Asn Asn Gln
        125                 130                 135

gat caa agt agc agt ctt cct gaa gaa tgt gta cct tca gat gaa agt   784
Asp Gln Ser Ser Ser Leu Pro Glu Glu Cys Val Pro Ser Asp Glu Ser
    140                 145                 150

act cct ccg agt att aaa aaa atc ata cat gtg ctg gag aag gtc cag   832
Thr Pro Pro Ser Ile Lys Lys Ile Ile His Val Leu Glu Lys Val Gln
155                 160                 165                 170

tat ctt gaa caa gaa gta gaa gaa ttt gta gga aaa aag aca gac aaa   880
Tyr Leu Glu Gln Glu Val Glu Glu Phe Val Gly Lys Lys Thr Asp Lys
                175                 180                 185

gca tac tgg ctt ctg gaa gaa atg cta acc aag gaa ctt ttg gaa ctg   928
Ala Tyr Trp Leu Leu Glu Glu Met Leu Thr Lys Glu Leu Leu Glu Leu
            190                 195                 200

gat tca gtt gaa act ggg ggc cag gac tct gta cgg cag gcc aga aaa   976
Asp Ser Val Glu Thr Gly Gly Gln Asp Ser Val Arg Gln Ala Arg Lys
        205                 210                 215

gag gct gtt tgt aag att cag gcc ata ttg gaa a                    1010
Glu Ala Val Cys Lys Ile Gln Ala Ile Leu Glu
    220                 225
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<210> 8
<211> 229
<212> PRT
<213> Homo sapiens

<400> 8

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Met Glu Met Val Ile Val Val Phe His Asn His Gly Arg Leu Tyr Asp
  1               5                  10                  15

His Lys Lys Asp Ala Trp Ala Ser Pro Gly Ala Tyr Gly Met Gly Gly
             20                  25                  30

Arg Tyr Pro Trp Pro Ser Ser Ala Pro Ser Ala Pro Pro Gly Asn Leu
         35                  40                  45
```


BNSDOCID <WO 0014106A1 A>

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Tyr Met Thr Glu Ser Thr Ser Pro Trp Pro Ser Ser Gly Ser Pro Gln
     50                  55                  60

Ser Pro Pro Ser Pro Pro Val Gln Gln Pro Lys Asp Ser Ser Tyr Pro
 65                  70                  75                  80

Tyr Ser Gln Ser Asp Gln Ser Met Asn Arg His Asn Phe Pro Cys Ser
                 85                  90                  95

Val His Gln Tyr Glu Ser Ser Gly Thr Val Asn Asn Asp Asp Ser Asp
            100                 105                 110

Leu Leu Asp Ser Gln Val Gln Tyr Ser Ala Glu Pro Gln Leu Tyr Gly
        115                 120                 125

Asn Ala Thr Ser Asp His Pro Asn Asn Gln Asp Gln Ser Ser Ser Leu
    130                 135                 140

Pro Glu Glu Cys Val Pro Ser Asp Glu Ser Thr Pro Pro Ser Ile Lys
145                 150                 155                 160

Lys Ile Ile His Val Leu Glu Lys Val Gln Tyr Leu Glu Gln Glu Val
                165                 170                 175

Glu Glu Phe Val Gly Lys Lys Thr Asp Lys Ala Tyr Trp Leu Leu Glu
            180                 185                 190

Glu Met Leu Thr Lys Glu Leu Leu Glu Leu Asp Ser Val Glu Thr Gly
        195                 200                 205

Gly Gln Asp Ser Val Arg Gln Ala Arg Lys Glu Ala Val Cys Lys Ile
    210                 215                 220

Gln Ala Ile Leu Glu
225
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<210> 9
<211> 689
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (3)..(482)

<220>
<221> unsure

BNSDOCID <WO 0014106A1 IA>

<222> (105)
<223> any amino acid

<400> 9

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ga gaa ata aaa aat gaa ctt ctc caa gca caa aac cct tct gaa ttg    47
   Glu Ile Lys Asn Glu Leu Leu Gln Ala Gln Asn Pro Ser Glu Leu
     1               5                  10                  15

tac ctg agc tcc aaa aca gaa ttg cag ggt tta att gga cag ttg gat   95
Tyr Leu Ser Ser Lys Thr Glu Leu Gln Gly Leu Ile Gly Gln Leu Asp
                20                  25                  30

gag gta agt ntt gaa aaa aac ccc tgc atc cgg gaa gcc agg aga aga   143
Glu Val Ser Xaa Glu Lys Asn Pro Cys Ile Arg Glu Ala Arg Arg Arg
            35                  40                  45

gca gtg atc gag gtg caa act ctg atc aca tat att gac ttg aag gag   191
Ala Val Ile Glu Val Gln Thr Leu Ile Thr Tyr Ile Asp Leu Lys Glu
        50                  55                  60

gcc ctt gag aaa aga aag ctg ttt gct tgt gag gag cac cca tcc cat   239
Ala Leu Glu Lys Arg Lys Leu Phe Ala Cys Glu Glu His Pro Ser His
    65                  70                  75

aaa gcc gtc tgg aac gtc ctt gga aac ttg tct gag atc cag gga gaa   287
Lys Ala Val Trp Asn Val Leu Gly Asn Leu Ser Glu Ile Gln Gly Glu
80                  85                  90                  95

gtt ctt tca ttt gat gga aat cga acc gat aag aac tac atc cgg ctg   335
Val Leu Ser Phe Asp Gly Asn Arg Thr Asp Lys Asn Tyr Ile Arg Leu
                100                 105                 110

gaa gag ctg ctc acc aag cag ctg cta gcc ctg gat gct gtt gat ccg   383
Glu Glu Leu Leu Thr Lys Gln Leu Leu Ala Leu Asp Ala Val Asp Pro
            115                 120                 125

cag gga gaa gag aag tgt aag gct gcc agg aaa caa gct gtg agg ctt   431
Gln Gly Glu Glu Lys Cys Lys Ala Ala Arg Lys Gln Ala Val Arg Leu
        130                 135                 140

gcg cag aat att ctc agc tat ctc gac ctg aaa tct gat gaa tgg gag   479
Ala Gln Asn Ile Leu Ser Tyr Leu Asp Leu Lys Ser Asp Glu Trp Glu
    145                 150                 155

tac tgaaatacca gagatctcac ttttgatact gttttgcact tcatatgtgc        532
Tyr
160
```


ENSDOCID <WO 0014106A1 A>

ttctatgtat agagagcttt cagttcattg atttatacgt gcatatttca gtctcagtat 592

ttatgattga agcaaattct attcagtatc tgctgctttt gatgttgcaa gacaaatatc 652

attatagcac gttaactttt ccattcggat caaaaaa 689

<210> 10
<211> 160
<212> PRT
<213> Homo sapiens

<400> 10

Glu Ile Lys Asn Glu Leu Leu Gln Ala Gln Asn Pro Ser Glu Leu Tyr
1 5 10 15

Leu Ser Ser Lys Thr Glu Leu Gln Gly Leu Ile Gly Gln Leu Asp Glu
20 25 30

Val Ser Xaa Glu Lys Asn Pro Cys Ile Arg Glu Ala Arg Arg Arg Ala
35 40 45

Val Ile Glu Val Gln Thr Leu Ile Thr Tyr Ile Asp Leu Lys Glu Ala
50 55 60

Leu Glu Lys Arg Lys Leu Phe Ala Cys Glu Glu His Pro Ser His Lys
65 70 75 80

Ala Val Trp Asn Val Leu Gly Asn Leu Ser Glu Ile Gln Gly Glu Val
85 90 95

Leu Ser Phe Asp Gly Asn Arg Thr Asp Lys Asn Tyr Ile Arg Leu Glu
100 105 110

Glu Leu Leu Thr Lys Gln Leu Leu Ala Leu Asp Ala Val Asp Pro Gln
115 120 125

Gly Glu Glu Lys Cys Lys Ala Ala Arg Lys Gln Ala Val Arg Leu Ala
130 135 140

Gln Asn Ile Leu Ser Tyr Leu Asp Leu Lys Ser Asp Glu Trp Glu Tyr
145 150 155 160

<210> 11
<211> 246
<212> DNA
<213> Caenorhabditis elegans

BNSDOCID <WO 0014106A1 IA>

<400> 11
atgtctttcc gcctcttcgt tgaaatattt cactttcttt tccagctttt tccccatctc 60

gaccigcttt ggtttttcga gaaaaccacg ttccaaatca gcgacatctc tcaaattgag 120

atcataggct ttttgaagat tgctcaaatt atgcttctca tattgcatga gcattttgaa 180

gcccgcgtca tcaaccaaag catttttttcc acccatcaca atgattttat catttcttt 240

aaaatt 246

<210> 12
<211> 210
<212> PRT
<213> Caenorhabditis elegans

<400> 12
Met Lys Val Asn Val Ser Cys Ser Ser Val Gln Thr Thr Ile Asp Ile
1 5 10 15

Leu Glu Glu Asn Gln Gly Glu Asp Glu Ser Ile Leu Thr Leu Gly Gln
20 25 30

Leu Arg Asp Arg Ile Ala Thr Asp Asn Asp Val Asp Val Glu Thr Met
35 40 45

Lys Leu Leu His Arg Gly Lys Phe Leu Gln Gly Ala Asp Asp Val Ser
50 55 60

Leu Ser Thr Leu Asn Phe Lys Glu Asn Asp Lys Ile Ile Val Met Gly
65 70 75 80

Gly Lys Asn Ala Leu Val Asp Asp Ala Gly Phe Lys Met Leu Met Gln
85 90 95

Tyr Glu Lys His Asn Leu Ser Asn Leu Gln Lys Ala Tyr Asp Leu Asn
100 105 110

Leu Arg Asp Val Ala Asp Leu Glu Arg Gly Phe Leu Glu Lys Pro Lys
115 120 125

Gln Val Glu Met Gly Lys Lys Leu Glu Lys Lys Val Lys Tyr Phe Asn
130 135 140

Glu Glu Ala Glu Arg His Leu Glu Thr Leu Asp Gly Met Asn Ile Ile
145 150 155 160

BNSDOCID <WO 0014106A1 IA>

```
Thr Glu Thr Thr Pro Glu Asn Gln Ala Lys Arg Asn Arg Glu Lys Arg
                165                 170                 175

Lys Thr Leu Val Asn Gly Ile Gln Thr Leu Leu Asn Gln Asn Asp Ala
            180                 185                 190

Leu Leu Arg Arg Leu Gln Glu Tyr Gln Ser Val Leu Asn Gly Asp Ile
        195                 200                 205

Pro Glu
    210
```

<210> 13
<211> 1377
<212> DNA
<213> Caenorhabditis elegans

<220>
<221> CDS
<222> (1)..(1377)

<400> 13

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atg cca gtc gtg aac ata cca atc aaa ata ctt ggt cag aat caa tca   48
Met Pro Val Val Asn Ile Pro Ile Lys Ile Leu Gly Gln Asn Gln Ser
  1               5                  10                  15

cat agt cga agt aac tcc tcg tct tct gtt gac aac gat cga aat caa   96
His Ser Arg Ser Asn Ser Ser Ser Ser Val Asp Asn Asp Arg Asn Gln
             20                  25                  30

cca cca cag cag cca cct caa ccg caa cca caa cag caa tct cag caa   144
Pro Pro Gln Gln Pro Pro Gln Pro Gln Pro Gln Gln Gln Ser Gln Gln
         35                  40                  45

caa tac cag cag gct cca aac gtg aat acc aat atg cat cat tcc aac   192
Gln Tyr Gln Gln Ala Pro Asn Val Asn Thr Asn Met His His Ser Asn
     50                  55                  60

gga ttc tca cct aac ttc cca tct cgt agt cct att ccg gac ttt ccc   240
Gly Phe Ser Pro Asn Phe Pro Ser Arg Ser Pro Ile Pro Asp Phe Pro
 65                  70                  75                  80

agt ttt tca tct ggg ttc cca aac gat tct gaa tgg tct tcg aat ttc   288
Ser Phe Ser Ser Gly Phe Pro Asn Asp Ser Glu Trp Ser Ser Asn Phe
                 85                  90                  95
```


BNSDOCID <WO 0014106A1 IA>

```
ccg tcg ttt cca aat ttc cca agt gga ttc tca aat gga agt tct aat   336
Pro Ser Phe Pro Asn Phe Pro Ser Gly Phe Ser Asn Gly Ser Ser Asn
            100                 105                 110

ttc cct gat ttt cca aga ttc gga aga gat gga gga cta tcg cca aac   384
Phe Pro Asp Phe Pro Arg Phe Gly Arg Asp Gly Gly Leu Ser Pro Asn
        115                 120                 125

cca ccg atg caa gga tac agg aga agt cca aca cca aca tca act caa   432
Pro Pro Met Gln Gly Tyr Arg Arg Ser Pro Thr Pro Thr Ser Thr Gln
    130                 135                 140

tct cca act tct aca tta aga cgc aac tct cag cag aat caa gct cct   480
Ser Pro Thr Ser Thr Leu Arg Arg Asn Ser Gln Gln Asn Gln Ala Pro
145                 150                 155                 160

cca caa tat tct cag caa caa cca caa caa gct caa caa cgt cag aca   528
Pro Gln Tyr Ser Gln Gln Gln Pro Gln Gln Ala Gln Gln Arg Gln Thr
                165                 170                 175

act cct ccg tca aca aaa gct tca tct cga cca cca tct cgt act cgt   576
Thr Pro Pro Ser Thr Lys Ala Ser Ser Arg Pro Pro Ser Arg Thr Arg
            180                 185                 190

gaa cca aag gaa cct gag gta ccc gag aga cca gca gtt att cca ttg   624
Glu Pro Lys Glu Pro Glu Val Pro Glu Arg Pro Ala Val Ile Pro Leu
        195                 200                 205

cca tat gag aag aag gag aaa cca ctg gag aag aaa ggt agt cgt gat   672
Pro Tyr Glu Lys Lys Glu Lys Pro Leu Glu Lys Lys Gly Ser Arg Asp
    210                 215                 220

tct gga aag ggt gat gag aac ctt gaa gag aac att gcc aag atc acg   720
Ser Gly Lys Gly Asp Glu Asn Leu Glu Glu Asn Ile Ala Lys Ile Thr
225                 230                 235                 240

atc gga aag aat aat tgc gag tta tgt ccg gaa caa gaa acg gac ggc   768
Ile Gly Lys Asn Asn Cys Glu Leu Cys Pro Glu Gln Glu Thr Asp Gly
                245                 250                 255

gac cca tct cca cta acc tcc cca atc acc gaa gga aag cca aag aga   816
Asp Pro Ser Pro Leu Thr Ser Pro Ile Thr Glu Gly Lys Pro Lys Arg
            260                 265                 270

gga aag aaa ctt caa cgt aat caa agt gtt gtt gat ttc aat gcc aag   864
Gly Lys Lys Leu Gln Arg Asn Gln Ser Val Val Asp Phe Asn Ala Lys
        275                 280                 285
```


BNSDOCID <WO 0014106A1 'A>

```
aca att gtt act ttg gat aaa att gaa tta caa gtt gag cag ttg aga   912
Thr Ile Val Thr Leu Asp Lys Ile Glu Leu Gln Val Glu Gln Leu Arg
    290                 295                 300

aaa aaa gct gct gaa ctc gaa atg gaa aaa gag caa att ctt cgt tct   960
Lys Lys Ala Ala Glu Leu Glu Met Glu Lys Glu Gln Ile Leu Arg Ser
305                 310                 315                 320

cta gga gaa atc agt gtt cat aac tgc atg ttc aaa ctg gaa gaa tgt   1008
Leu Gly Glu Ile Ser Val His Asn Cys Met Phe Lys Leu Glu Glu Cys
                325                 330                 335

gat cgt gaa gag att gaa gca atc act gac cga ttg aca aaa aga aca   1056
Asp Arg Glu Glu Ile Glu Ala Ile Thr Asp Arg Leu Thr Lys Arg Thr
            340                 345                 350

aag aca gtt caa gtt gtt gtc gaa act cca cga aat gaa gaa cag aaa   1104
Lys Thr Val Gln Val Val Val Glu Thr Pro Arg Asn Glu Glu Gln Lys
        355                 360                 365

aaa gca ctg gaa gat gca act ttg atg atc gat gaa gtc gga gaa atg   1152
Lys Ala Leu Glu Asp Ala Thr Leu Met Ile Asp Glu Val Gly Glu Met
    370                 375                 380

atg cat tcg aat att gaa aag gct aag ctg tgc cta caa acc tac atg   1200
Met His Ser Asn Ile Glu Lys Ala Lys Leu Cys Leu Gln Thr Tyr Met
385                 390                 395                 400

aac gcc tgt tcg tac gaa gaa act gct gga gcc acc tgc caa aac ttc   1248
Asn Ala Cys Ser Tyr Glu Glu Thr Ala Gly Ala Thr Cys Gln Asn Phe
                405                 410                 415

ttg aag atc ata att cag tgc gct gct gat gat cag aaa cgc atc aag   1296
Leu Lys Ile Ile Ile Gln Cys Ala Ala Asp Asp Gln Lys Arg Ile Lys
            420                 425                 430

cgt cgt ctg gaa aat ctg atg tct caa att gag aat gct gag aga acg   1344
Arg Arg Leu Glu Asn Leu Met Ser Gln Ile Glu Asn Ala Glu Arg Thr
        435                 440                 445

aaa gca gat ttg atg gat gat caa agc gaa tag                      1377
Lys Ala Asp Leu Met Asp Asp Gln Ser Glu
    450                 455
```

<210> 14
<211> 458
<212> PRT

BNSDOCID <WO 0014106A1 IA>

<213> Caenorhabditis elegans

<400> 14

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Met Pro Val Val Asn Ile Pro Ile Lys Ile Leu Gly Gln Asn Gln Ser
 1               5                  10                  15

His Ser Arg Ser Asn Ser Ser Ser Ser Val Asp Asn Asp Arg Asn Gln
            20                  25                  30

Pro Pro Gln Gln Pro Pro Gln Pro Gln Pro Gln Gln Gln Ser Gln Gln
        35                  40                  45

Gln Tyr Gln Gln Ala Pro Asn Val Asn Thr Asn Met His His Ser Asn
    50                  55                  60

Gly Phe Ser Pro Asn Phe Pro Ser Arg Ser Pro Ile Pro Asp Phe Pro
65                  70                  75                  80

Ser Phe Ser Ser Gly Phe Pro Asn Asp Ser Glu Trp Ser Ser Asn Phe
                85                  90                  95

Pro Ser Phe Pro Asn Phe Pro Ser Gly Phe Ser Asn Gly Ser Ser Asn
            100                 105                 110

Phe Pro Asp Phe Pro Arg Phe Gly Arg Asp Gly Gly Leu Ser Pro Asn
        115                 120                 125

Pro Pro Met Gln Gly Tyr Arg Arg Ser Pro Thr Pro Thr Ser Thr Gln
    130                 135                 140

Ser Pro Thr Ser Thr Leu Arg Arg Asn Ser Gln Gln Asn Gln Ala Pro
145                 150                 155                 160

Pro Gln Tyr Ser Gln Gln Gln Pro Gln Gln Ala Gln Gln Arg Gln Thr
                165                 170                 175

Thr Pro Pro Ser Thr Lys Ala Ser Ser Arg Pro Pro Ser Arg Thr Arg
            180                 185                 190

Glu Pro Lys Glu Pro Glu Val Pro Glu Arg Pro Ala Val Ile Pro Leu
        195                 200                 205

Pro Tyr Glu Lys Lys Glu Lys Pro Leu Glu Lys Lys Gly Ser Arg Asp
    210                 215                 220

Ser Gly Lys Gly Asp Glu Asn Leu Glu Glu Asn Ile Ala Lys Ile Thr
225                 230                 235                 240
```


BNSDOCID <WO__0014106A1_IA>

```
Ile Gly Lys Asn Asn Cys Glu Leu Cys Pro Glu Gln Glu Thr Asp Gly
                245                 250                 255

Asp Pro Ser Pro Leu Thr Ser Pro Ile Thr Glu Gly Lys Pro Lys Arg
            260                 265                 270

Gly Lys Lys Leu Gln Arg Asn Gln Ser Val Val Asp Phe Asn Ala Lys
        275                 280                 285

Thr Ile Val Thr Leu Asp Lys Ile Glu Leu Gln Val Glu Gln Leu Arg
    290                 295                 300

Lys Lys Ala Ala Glu Leu Glu Met Glu Lys Glu Gln Ile Leu Arg Ser
305                 310                 315                 320

Leu Gly Glu Ile Ser Val His Asn Cys Met Phe Lys Leu Glu Glu Cys
                325                 330                 335

Asp Arg Glu Glu Ile Glu Ala Ile Thr Asp Arg Leu Thr Lys Arg Thr
            340                 345                 350

Lys Thr Val Gln Val Val Val Glu Thr Pro Arg Asn Glu Glu Gln Lys
        355                 360                 365

Lys Ala Leu Glu Asp Ala Thr Leu Met Ile Asp Glu Val Gly Glu Met
    370                 375                 380

Met His Ser Asn Ile Glu Lys Ala Lys Leu Cys Leu Gln Thr Tyr Met
385                 390                 395                 400

Asn Ala Cys Ser Tyr Glu Glu Thr Ala Gly Ala Thr Cys Gln Asn Phe
                405                 410                 415

Leu Lys Ile Ile Ile Gln Cys Ala Ala Asp Asp Gln Lys Arg Ile Lys
            420                 425                 430

Arg Arg Leu Glu Asn Leu Met Ser Gln Ile Glu Asn Ala Glu Arg Thr
        435                 440                 445

Lys Ala Asp Leu Met Asp Asp Gln Ser Glu
    450                 455
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<210> 15
<211> 588
<212> DNA
<213> Schizosaccharomyces pombe

BNSDOCID <WO 0014106A1 IA>

<220>
<221> CDS
<222> (1)..(588)

<400> 15

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atg tca gaa aag act agc aca gtt aca ata cac tat gga aat cag cga   48
Met Ser Glu Lys Thr Ser Thr Val Thr Ile His Tyr Gly Asn Gln Arg
  1               5                  10                  15

ttt ccg gta gca gtc aat cta aat gag acg tta agt gaa ctg att gat   96
Phe Pro Val Ala Val Asn Leu Asn Glu Thr Leu Ser Glu Leu Ile Asp
             20                  25                  30

gat tta ctt gaa acg act gag att tct gag aag aaa gtc aag ctt ttt   144
Asp Leu Leu Glu Thr Thr Glu Ile Ser Glu Lys Lys Val Lys Leu Phe
         35                  40                  45

tac gct ggc aag cgt tta aaa gac aaa aaa gcc tcg tta tca aaa ttg   192
Tyr Ala Gly Lys Arg Leu Lys Asp Lys Lys Ala Ser Leu Ser Lys Leu
     50                  55                  60

ggt tta aaa aat cat agt aaa att cta tgt ata aga cca cat aag caa   240
Gly Leu Lys Asn His Ser Lys Ile Leu Cys Ile Arg Pro His Lys Gln
 65                  70                  75                  80

caa cga ggt tcc aag gaa aaa gac acg gtt gag ccc gct ccg aaa gcg   288
Gln Arg Gly Ser Lys Glu Lys Asp Thr Val Glu Pro Ala Pro Lys Ala
                 85                  90                  95

gaa gcg gag aat cct gta ttt tcg cgt att tct gga gaa ata aaa gcc   336
Glu Ala Glu Asn Pro Val Phe Ser Arg Ile Ser Gly Glu Ile Lys Ala
            100                 105                 110

atc gat cag tat gtt gac aaa gaa ctt tcc ccc atg tac gac aat tac   384
Ile Asp Gln Tyr Val Asp Lys Glu Leu Ser Pro Met Tyr Asp Asn Tyr
        115                 120                 125

gta aat aaa ccg tcg aac gat cca aag cag aaa aac aaa cag aaa cta   432
Val Asn Lys Pro Ser Asn Asp Pro Lys Gln Lys Asn Lys Gln Lys Leu
    130                 135                 140

atg ata agt gaa cta ctt tta caa cag ctt tta aaa ttg gat gga gtt   480
Met Ile Ser Glu Leu Leu Leu Gln Gln Leu Leu Lys Leu Asp Gly Val
145                 150                 155                 160

gac gta ctg ggc agc gag aaa ttg cgt ttt gaa cgg aag caa ctt gtt   528
Asp Val Leu Gly Ser Glu Lys Leu Arg Phe Glu Arg Lys Gln Leu Val
                165                 170                 175
```


BNSDOCID <WO 0014106A1 IA>

tct aag atc caa aaa atg ttg gat cac gtt gac caa aca agc caa gaa 576
Ser Lys Ile Gln Lys Met Leu Asp His Val Asp Gln Thr Ser Gln Glu
180 185 190

gtg gcc gca tag 588
Val Ala Ala
195

<210> 16
<211> 195
<212> PRT
<213> Schizosaccharomyces pombe

<400> 16
Met Ser Glu Lys Thr Ser Thr Val Thr Ile His Tyr Gly Asn Gln Arg
1 5 10 15

Phe Pro Val Ala Val Asn Leu Asn Glu Thr Leu Ser Glu Leu Ile Asp
20 25 30

Asp Leu Leu Glu Thr Thr Glu Ile Ser Glu Lys Lys Val Lys Leu Phe
35 40 45

Tyr Ala Gly Lys Arg Leu Lys Asp Lys Lys Ala Ser Leu Ser Lys Leu
50 55 60

Gly Leu Lys Asn His Ser Lys Ile Leu Cys Ile Arg Pro His Lys Gln
65 70 75 80

Gln Arg Gly Ser Lys Glu Lys Asp Thr Val Glu Pro Ala Pro Lys Ala
85 90 95

Glu Ala Glu Asn Pro Val Phe Ser Arg Ile Ser Gly Glu Ile Lys Ala
100 105 110

Ile Asp Gln Tyr Val Asp Lys Glu Leu Ser Pro Met Tyr Asp Asn Tyr
115 120 125

Val Asn Lys Pro Ser Asn Asp Pro Lys Gln Lys Asn Lys Gln Lys Leu
130 135 140

Met Ile Ser Glu Leu Leu Leu Gln Gln Leu Leu Lys Leu Asp Gly Val
145 150 155 160

Asp Val Leu Gly Ser Glu Lys Leu Arg Phe Glu Arg Lys Gln Leu Val
165 170 175

BNSDOCID <WO 0014106A1 IA>

```
Ser Lys Ile Gln Lys Met Leu Asp His Val Asp Gln Thr Ser Gln Glu
            180                 185                 190

Val Ala Ala
        195


<210> 17
<211> 621
<212> DNA
<213> Schizosaccharomyces pombe

<220>
<221> CDS
<222> (1)..(621)

<400> 17
atg tct ttt ttt acc cag ttg tgt tct atg gat aaa aaa tat tgg atc   48
Met Ser Phe Phe Thr Gln Leu Cys Ser Met Asp Lys Lys Tyr Trp Ile
  1               5                  10                  15

tct cta gct gta ttg tca gtt act gtt ttg att agc gca tta ttg aaa   96
Ser Leu Ala Val Leu Ser Val Thr Val Leu Ile Ser Ala Leu Leu Lys
            20                  25                  30

aag aga gct act gaa acc gaa gat att gtc gtt gtt cat tac gat ggc   144
Lys Arg Ala Thr Glu Thr Glu Asp Ile Val Val Val His Tyr Asp Gly
        35                  40                  45

gaa aag ttg aat ttt gtg ttg cga caa cca agg ctg aat atg gtt tct   192
Glu Lys Leu Asn Phe Val Leu Arg Gln Pro Arg Leu Asn Met Val Ser
    50                  55                  60

tac act agt ttt ctt cgt cgc gtg tgc aac gca ttt tca gta atg ccc   240
Tyr Thr Ser Phe Leu Arg Arg Val Cys Asn Ala Phe Ser Val Met Pro
65                  70                  75                  80

gac aaa gcg tct ctc aag tta aac ggg gtg acc ctc aag gat ggt tca   288
Asp Lys Ala Ser Leu Lys Leu Asn Gly Val Thr Leu Lys Asp Gly Ser
                85                  90                  95

ctt tcc gac caa aat gtg caa aat gga agt gaa tta gag ctc gaa tta   336
Leu Ser Asp Gln Asn Val Gln Asn Gly Ser Glu Leu Glu Leu Glu Leu
            100                 105                 110

ccc aaa ctg agc ccg gca atg caa caa att gaa gca tat ata gat gag   384
Pro Lys Leu Ser Pro Ala Met Gln Gln Ile Glu Ala Tyr Ile Asp Glu
```


BNSDOCID <WO 0014106A1_IA>

```
        115                 120                 125

ctt caa cag gat ctc gtc cct aaa att gaa gcc ttc tgc caa tcg tct   432
Leu Gln Gln Asp Leu Val Pro Lys Ile Glu Ala Phe Cys Gln Ser Ser
    130                 135                 140

ccc gct tcg gca caa gat gtt caa gat ttg cat aca cgc ctt agt gaa   480
Pro Ala Ser Ala Gln Asp Val Gln Asp Leu His Thr Arg Leu Ser Glu
145                 150                 155                 160

aca ttg ttg gct agg atg ata aaa tta gat gct gtt aat gtt gaa gac   528
Thr Leu Leu Ala Arg Met Ile Lys Leu Asp Ala Val Asn Val Glu Asp
                165                 170                 175

gac cca gaa gct cgt ctt aaa aga aaa gaa gct att cgt tta tct caa   576
Asp Pro Glu Ala Arg Leu Lys Arg Lys Glu Ala Ile Arg Leu Ser Gln
            180                 185                 190

caa tat ttg agt aaa cta gat tcc acc aag aat caa aac aaa tga       621
Gln Tyr Leu Ser Lys Leu Asp Ser Thr Lys Asn Gln Asn Lys
        195                 200                 205
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<210> 18
<211> 206
<212> PRT
<213> Schizosaccharomyces pombe

<400> 18

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Met Ser Phe Phe Thr Gln Leu Cys Ser Met Asp Lys Lys Tyr Trp Ile
  1               5                  10                  15

Ser Leu Ala Val Leu Ser Val Thr Val Leu Ile Ser Ala Leu Leu Lys
             20                  25                  30

Lys Arg Ala Thr Glu Thr Glu Asp Ile Val Val Val His Tyr Asp Gly
         35                  40                  45

Glu Lys Leu Asn Phe Val Leu Arg Gln Pro Arg Leu Asn Met Val Ser
     50                  55                  60

Tyr Thr Ser Phe Leu Arg Arg Val Cys Asn Ala Phe Ser Val Met Pro
 65                  70                  75                  80

Asp Lys Ala Ser Leu Lys Leu Asn Gly Val Thr Leu Lys Asp Gly Ser
                 85                  90                  95

Leu Ser Asp Gln Asn Val Gln Asn Gly Ser Glu Leu Glu Leu Glu Leu
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BNSDOCID <WO 0014106A1 IA>

100 105 110

Pro Lys Leu Ser Pro Ala Met Gln Gln Ile Glu Ala Tyr Ile Asp Glu
115 120 125

Leu Gln Gln Asp Leu Val Pro Lys Ile Glu Ala Phe Cys Gln Ser Ser
130 135 140

Pro Ala Ser Ala Gln Asp Val Gln Asp Leu His Thr Arg Leu Ser Glu
145 150 155 160

Thr Leu Leu Ala Arg Met Ile Lys Leu Asp Ala Val Asn Val Glu Asp
165 170 175

Asp Pro Glu Ala Arg Leu Lys Arg Lys Glu Ala Ile Arg Leu Ser Gln
180 185 190

Gln Tyr Leu Ser Lys Leu Asp Ser Thr Lys Asn Gln Asn Lys
195 200 205

<210> 19
<211> 2534
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (307)..(2034)

<400> 19
gcggagctcc gcatccaacc ccgggccgcg gccaacttct ctggactgga ccagaagttt 60

ctagccggcc agttgctacc tccctttatc tcctccttcc cctctggcag cgaggaggct 120

atttccagac acttccaccc ctctctggcc acgtcacccc cgcctttaat tcataaaggt 180

gcccggcgcc ggcttcccgg acacgtcggc ggcggagagg ggcccacggc ggcggcccgg 240

ccagagactc ggcgcccgga gccagcgccc cgcacccgcg ccccagcggg cagaccccaa 300

cccagc atg agc gcc gcc acc cac tcg ccc atg atg cag gtg gcg tcc 348
Met Ser Ala Ala Thr His Ser Pro Met Met Gln Val Ala Ser
1 5 10

ggc aac ggt gac cgc gac cct ttg ccc ccc gga tgg gag atc aag atc 396
Gly Asn Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp Glu Ile Lys Ile
15 20 25 30

BNSDOCID <WO 0014106A1_IA>

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gac ccg cag acc ggc tgg ccc ttc ttc gtg gac cac aac agc cgc acc   444
Asp Pro Gln Thr Gly Trp Pro Phe Phe Val Asp His Asn Ser Arg Thr
                35                  40                  45

act acg tgg aac gac ccg cgc gtg ccc tct gag ggc ccc aag gag act   492
Thr Thr Trp Asn Asp Pro Arg Val Pro Ser Glu Gly Pro Lys Glu Thr
            50                  55                  60

cca tcc tct gcc aat ggc cct tcc cgg gag ggc tct agg ctg ccg cct   540
Pro Ser Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser Arg Leu Pro Pro
        65                  70                  75

gct agg gaa ggc cac cct gtg tac ccc cag ctc cga cca ggc tac att   588
Ala Arg Glu Gly His Pro Val Tyr Pro Gln Leu Arg Pro Gly Tyr Ile
    80                  85                  90

ccc att cct gtg ctc cat gaa ggc gct gag aac cgg cag gtg cac cct   636
Pro Ile Pro Val Leu His Glu Gly Ala Glu Asn Arg Gln Val His Pro
95                  100                 105                 110

ttc cat gtc tat ccc cag cct ggg atg cag cga ttc cga act gag gcg   684
Phe His Val Tyr Pro Gln Pro Gly Met Gln Arg Phe Arg Thr Glu Ala
                115                 120                 125

gca gca gcg gct cct cag agg tcc cag tca cct ctg cgg ggc atg cca   732
Ala Ala Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu Arg Gly Met Pro
            130                 135                 140

gaa acc act cag cca gat aaa cag tgt gga cag gtg gca gcg gcg gcg   780
Glu Thr Thr Gln Pro Asp Lys Gln Cys Gly Gln Val Ala Ala Ala Ala
        145                 150                 155

gca gcc cag ccc cca gcc tcc cac gga cct gag cgg tcc cag tct cca   828
Ala Ala Gln Pro Pro Ala Ser His Gly Pro Glu Arg Ser Gln Ser Pro
    160                 165                 170

gct gcc tct gac tgc tca tcc tca tcc tcc tcg gcc agc ctg cct tcc   876
Ala Ala Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala Ser Leu Pro Ser
175                 180                 185                 190

tcc ggc agg agc agc ctg ggc agt cac cag ctc ccg cgg ggg tac atc   924
Ser Gly Arg Ser Ser Leu Gly Ser His Gln Leu Pro Arg Gly Tyr Ile
                195                 200                 205

tcc att ccg gtg ata cac gag cag aac gtt acc cgg cca gca gcc cag   972
Ser Ile Pro Val Ile His Glu Gln Asn Val Thr Arg Pro Ala Ala Gln
            210                 215                 220
```


BNSDOCID <WO 0014106A1 IA>

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ccc tcc ttc cac aaa gcc cag aag acg cac tac cca gcg cag agg ggt   1020
Pro Ser Phe His Lys Ala Gln Lys Thr His Tyr Pro Ala Gln Arg Gly
        225                 230                 235

gag tac cag acc cac cag cct gtg tac cac aag atc cag ggg gat gac   1068
Glu Tyr Gln Thr His Gln Pro Val Tyr His Lys Ile Gln Gly Asp Asp
    240                 245                 250

tgg gag ccc cgg ccc ctg cgg gcg gca tcc ccg ttc agg tca tct gtc   1116
Trp Glu Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe Arg Ser Ser Val
255                 260                 265                 270

cag ggt gca tcg agc cgg gag ggc tca cca gcc agg agc agc acg cca   1164
Gln Gly Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg Ser Ser Thr Pro
                275                 280                 285

ctc cac tcc ccc tcg ccc atc cgt gtg cac acc gtg gtc gac agg cct   1212
Leu His Ser Pro Ser Pro Ile Arg Val His Thr Val Val Asp Arg Pro
            290                 295                 300

cag cag ccc atg acc cat cga gaa act gca cct gtt tcc cag cct gaa   1260
Gln Gln Pro Met Thr His Arg Glu Thr Ala Pro Val Ser Gln Pro Glu
        305                 310                 315

aac aaa cca gaa agt aag cca ggc cca gtt gga cca gaa ctc cct cct   1308
Asn Lys Pro Glu Ser Lys Pro Gly Pro Val Gly Pro Glu Leu Pro Pro
    320                 325                 330

gga cac atc cca att caa gtg atc cgc aaa gag gtg gat tct aaa cct   1356
Gly His Ile Pro Ile Gln Val Ile Arg Lys Glu Val Asp Ser Lys Pro
335                 340                 345                 350

gtt tcc cag aag ccc cca cct ccc tct gag aag gta gag gtg aaa gtt   1404
Val Ser Gln Lys Pro Pro Pro Pro Ser Glu Lys Val Glu Val Lys Val
                355                 360                 365

ccc cct gct cca gtt cct tgt cct cct ccc agc cct ggc cct tct gct   1452
Pro Pro Ala Pro Val Pro Cys Pro Pro Pro Ser Pro Gly Pro Ser Ala
            370                 375                 380

gtc ccc tct tcc ccc aag agt gtg gct aca gaa gag agg gca gcc ccc   1500
Val Pro Ser Ser Pro Lys Ser Val Ala Thr Glu Glu Arg Ala Ala Pro
        385                 390                 395

agc act gcc cct gca gaa gct aca cct cca aaa cca gga gaa gcc gag   1548
Ser Thr Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro Gly Glu Ala Glu
    400                 405                 410
```


BNSDOCID <WO 0014106A1 IA>

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gct ccc cca aaa cat cca gga gtg ctg aaa gtg gaa gcc atc ctg gag   1596
Ala Pro Pro Lys His Pro Gly Val Leu Lys Val Glu Ala Ile Leu Glu
415                 420                 425                 430

aag gtg cag ggg ctg gag cag gct gta gac aac ttt gaa ggc aag aag   1644
Lys Val Gln Gly Leu Glu Gln Ala Val Asp Asn Phe Glu Gly Lys Lys
                435                 440                 445

act gac aaa aag tac ctg atg atc gaa gag tat ttg acc aaa gag ctg   1692
Thr Asp Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu Thr Lys Glu Leu
            450                 455                 460

ctg gcc ctg gat tca gtg gac ccc gag gga cga gcc gat gtg cgt cag   1740
Leu Ala Leu Asp Ser Val Asp Pro Glu Gly Arg Ala Asp Val Arg Gln
        465                 470                 475

gcc agg aga gac ggt gtc agg aag gtt cag acc atc ttg gaa aaa ctt   1788
Ala Arg Arg Asp Gly Val Arg Lys Val Gln Thr Ile Leu Glu Lys Leu
    480                 485                 490

gaa cag aaa gcc att gat gtc cca ggt caa gtc cag gtc tat gaa ctc   1836
Glu Gln Lys Ala Ile Asp Val Pro Gly Gln Val Gln Val Tyr Glu Leu
495                 500                 505                 510

cag ccc agc aac ctt gaa gca gat cag cca ctg cag gca atc atg gag   1884
Gln Pro Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln Ala Ile Met Glu
                515                 520                 525

atg ggt gcc gtg gca gca gac aag ggc aag aaa aat gct gga aat gca   1932
Met Gly Ala Val Ala Ala Asp Lys Gly Lys Lys Asn Ala Gly Asn Ala
            530                 535                 540

gaa gat ccc cac aca gaa acc cag cag cca gaa gcc aca gca gca gcg   1980
Glu Asp Pro His Thr Glu Thr Gln Gln Pro Glu Ala Thr Ala Ala Ala
        545                 550                 555

act tca aac ccc agc agc atg aca gac acc cct ggt aac cca gca gca   2028
Thr Ser Asn Pro Ser Ser Met Thr Asp Thr Pro Gly Asn Pro Ala Ala
    560                 565                 570

ccg tag cctctgccct gtaaaaatca gactcggaac cgatgtgtgc tttagggaat    2084
Pro
575

tttaagttgc atgcatttca gagactttaa gtcagttggt ttttattagc tgcttggtat 2144

gcagtaactt gggtggaggc aaaacactaa taaaagggct aaaaaggaaa atgatgcttt 2204
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BNSDOCID <WO 0014106A1 IA>

tctttctatat tcttactctg tacaaataaa gaagttgctt gttgtttgag aagtttaacc 2264

ccgttgcttg ttctgcagcc ctgtctactt gggcaccccc accacctgtt agctgtggtt 2324

gtgcactgtc ttttgtagct ctggactgga ggggtagatg gggagtcaat tacccatcac 2384

ataaatatga aacatttatc agaaatgttg ccattttaat gagatgattt tcttcatctc 2444

ataattaaaa tacctgactt tagagagagt aaaatgtgcc aggagccata ggaatatctg 2504

tatgttggat gactttaatg ctacattttc 2534

<210> 20
<211> 575
<212> PRT
<213> Homo sapiens

<400> 20

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Met Ser Ala Ala Thr His Ser Pro Met Met Gln Val Ala Ser Gly Asn
  1               5                  10                  15

Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp Glu Ile Lys Ile Asp Pro
             20                  25                  30

Gln Thr Gly Trp Pro Phe Phe Val Asp His Asn Ser Arg Thr Thr Thr
         35                  40                  45

Trp Asn Asp Pro Arg Val Pro Ser Glu Gly Pro Lys Glu Thr Pro Ser
     50                  55                  60

Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser Arg Leu Pro Pro Ala Arg
 65                  70                  75                  80

Glu Gly His Pro Val Tyr Pro Gln Leu Arg Pro Gly Tyr Ile Pro Ile
                 85                  90                  95

Pro Val Leu His Glu Gly Ala Glu Asn Arg Gln Val His Pro Phe His
            100                 105                 110

Val Tyr Pro Gln Pro Gly Met Gln Arg Phe Arg Thr Glu Ala Ala Ala
        115                 120                 125

Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu Arg Gly Met Pro Glu Thr
    130                 135                 140

Thr Gln Pro Asp Lys Gln Cys Gly Gln Val Ala Ala Ala Ala Ala Ala
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BNSDOCID <WO 0014106A1 IA>

145 150 155 160

Gln Pro Pro Ala Ser His Gly Pro Glu Arg Ser Gln Ser Pro Ala Ala
165 170 175

Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala Ser Leu Pro Ser Ser Gly
180 185 190

Arg Ser Ser Leu Gly Ser His Gln Leu Pro Arg Gly Tyr Ile Ser Ile
195 200 205

Pro Val Ile His Glu Gln Asn Val Thr Arg Pro Ala Ala Gln Pro Ser
210 215 220

Phe His Lys Ala Gln Lys Thr His Tyr Pro Ala Gln Arg Gly Glu Tyr
225 230 235 240

Gln Thr His Gln Pro Val Tyr His Lys Ile Gln Gly Asp Asp Trp Glu
245 250 255

Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe Arg Ser Ser Val Gln Gly
260 265 270

Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg Ser Ser Thr Pro Leu His
275 280 285

Ser Pro Ser Pro Ile Arg Val His Thr Val Val Asp Arg Pro Gln Gln
290 295 300

Pro Met Thr His Arg Glu Thr Ala Pro Val Ser Gln Pro Glu Asn Lys
305 310 315 320

Pro Glu Ser Lys Pro Gly Pro Val Gly Pro Glu Leu Pro Pro Gly His
325 330 335

Ile Pro Ile Gln Val Ile Arg Lys Glu Val Asp Ser Lys Pro Val Ser
340 345 350

Gln Lys Pro Pro Pro Pro Ser Glu Lys Val Glu Val Lys Val Pro Pro
355 360 365

Ala Pro Val Pro Cys Pro Pro Pro Ser Pro Gly Pro Ser Ala Val Pro
370 375 380

Ser Ser Pro Lys Ser Val Ala Thr Glu Glu Arg Ala Ala Pro Ser Thr
385 390 395 400

Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro Gly Glu Ala Glu Ala Pro

BNSDOCID <WO 0014106A1 IA>

405 410 415

Pro Lys His Pro Gly Val Leu Lys Val Glu Ala Ile Leu Glu Lys Val
420 425 430

Gln Gly Leu Glu Gln Ala Val Asp Asn Phe Glu Gly Lys Lys Thr Asp
435 440 445

Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu Thr Lys Glu Leu Leu Ala
450 455 460

Leu Asp Ser Val Asp Pro Glu Gly Arg Ala Asp Val Arg Gln Ala Arg
465 470 475 480

Arg Asp Gly Val Arg Lys Val Gln Thr Ile Leu Glu Lys Leu Glu Gln
485 490 495

Lys Ala Ile Asp Val Pro Gly Gln Val Gln Val Tyr Glu Leu Gln Pro
500 505 510

Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln Ala Ile Met Glu Met Gly
515 520 525

Ala Val Ala Ala Asp Lys Gly Lys Lys Asn Ala Gly Asn Ala Glu Asp
530 535 540

Pro His Thr Glu Thr Gln Gln Pro Glu Ala Thr Ala Ala Ala Thr Ser
545 550 555 560

Asn Pro Ser Ser Met Thr Asp Thr Pro Gly Asn Pro Ala Ala Pro
565 570 575

<210> 21
<211> 1966
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (43)..(1416)

<400> 21
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Met Ser Ala Leu
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agg cgc tcg ggc tac ggc ccc agt gac ggt ccg tcc tac ggc cgc tac 102

BNSDOCID <WO_ _0014106A1 A>

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Arg Arg Ser Gly Tyr Gly Pro Ser Asp Gly Pro Ser Tyr Gly Arg Tyr
  5                  10                  15                  20

tac ggg cct ggg ggt gga gat gtg ccg gta cac cca cct cca ccc tta   150
Tyr Gly Pro Gly Gly Gly Asp Val Pro Val His Pro Pro Pro Pro Leu
                  25                  30                  35

tat cct ctt cgc cct gaa cct ccc cag cct ccc att tcc tgg cgg gtg   198
Tyr Pro Leu Arg Pro Glu Pro Pro Gln Pro Pro Ile Ser Trp Arg Val
              40                  45                  50

cgc ggg ggc ggc ccg gcg gag acc acc tgg ctg gga gaa ggc gga gga   246
Arg Gly Gly Gly Pro Ala Glu Thr Thr Trp Leu Gly Glu Gly Gly Gly
          55                  60                  65

ggc gat ggc tac tat ccc tcg gga ggc gcc tgg cca gag cct ggt cga   294
Gly Asp Gly Tyr Tyr Pro Ser Gly Gly Ala Trp Pro Glu Pro Gly Arg
      70                  75                  80

gcc gga gga agc cac cag gag cag cca cca tat cct agc tac aat tct   342
Ala Gly Gly Ser His Gln Glu Gln Pro Pro Tyr Pro Ser Tyr Asn Ser
  85                  90                  95                  100

aac tat tgg aat tct act gcg aga tct agg gct cct tac cca agt aca   390
Asn Tyr Trp Asn Ser Thr Ala Arg Ser Arg Ala Pro Tyr Pro Ser Thr
                 105                 110                 115

tat cct gta aga cca gaa ttg caa ggc cag agt ttg aat tct tat aca   438
Tyr Pro Val Arg Pro Glu Leu Gln Gly Gln Ser Leu Asn Ser Tyr Thr
             120                 125                 130

aat gga gcg tat ggt cca aca tac ccc cca ggc cct ggg gca aat act   486
Asn Gly Ala Tyr Gly Pro Thr Tyr Pro Pro Gly Pro Gly Ala Asn Thr
         135                 140                 145

gcc tca tac tca ggg gct tat tat gca cct ggt tat act cag acc agt   534
Ala Ser Tyr Ser Gly Ala Tyr Tyr Ala Pro Gly Tyr Thr Gln Thr Ser
     150                 155                 160

tac tcc aca gaa gtt cca agt act tac cgt tca tct ggc aac agc cca   582
Tyr Ser Thr Glu Val Pro Ser Thr Tyr Arg Ser Ser Gly Asn Ser Pro
165                 170                 175                 180

act cca gtc tct cgt tgg atc tat ccc cag cag gac tgt cag act gaa   630
Thr Pro Val Ser Arg Trp Ile Tyr Pro Gln Gln Asp Cys Gln Thr Glu
                 185                 190                 195

gca ccc cct ctt agg ggg cag gtt cca gga tat ccg cct tca cag aac   678
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BNSDOCID <WO 0014106A1 IA>

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Ala Pro Pro Leu Arg Gly Gln Val Pro Gly Tyr Pro Pro Ser Gln Asn
            200                 205                 210

cct gga atg acc ctg ccc cat tat cct tat gga gat ggt aat cgt agt   726
Pro Gly Met Thr Leu Pro His Tyr Pro Tyr Gly Asp Gly Asn Arg Ser
        215                 220                 225

gtt cca caa tca gga ccg act gta cga cca caa gaa gat gcg tgg gct   774
Val Pro Gln Ser Gly Pro Thr Val Arg Pro Gln Glu Asp Ala Trp Ala
    230                 235                 240

tct cct ggt gct tat gga atg ggt ggc cgt tat ccc tgg cct tca tca   822
Ser Pro Gly Ala Tyr Gly Met Gly Gly Arg Tyr Pro Trp Pro Ser Ser
245                 250                 255                 260

gcg ccc tca gca cca ccc ggc aat ctc tac atg act gaa agt act tca   870
Ala Pro Ser Ala Pro Pro Gly Asn Leu Tyr Met Thr Glu Ser Thr Ser
                265                 270                 275

cca tgg cct agc agt ggc tct ccc cag tca ccc cct tca ccc cca gtc   918
Pro Trp Pro Ser Ser Gly Ser Pro Gln Ser Pro Pro Ser Pro Pro Val
            280                 285                 290

cag cag ccc aag gat tct tca tac ccc tat agc caa tca gat caa agc   966
Gln Gln Pro Lys Asp Ser Ser Tyr Pro Tyr Ser Gln Ser Asp Gln Ser
        295                 300                 305

atg aac cgg cac aac ttt cct tgc agt gtc cat cag tac gaa tcc tcg   1014
Met Asn Arg His Asn Phe Pro Cys Ser Val His Gln Tyr Glu Ser Ser
    310                 315                 320

ggg aca gtg atc aat gaa gat tca gat ctt ttg gat tcc caa gtc cag   1062
Gly Thr Val Ile Asn Glu Asp Ser Asp Leu Leu Asp Ser Gln Val Gln
325                 330                 335                 340

tat agt gct gag cct cag ctg tat ggt aat gcc acc agt gac cat ccc   1110
Tyr Ser Ala Glu Pro Gln Leu Tyr Gly Asn Ala Thr Ser Asp His Pro
                345                 350                 355

aac aat caa gat caa agt agc agt ctt cct gaa gaa tgt gta cct tca   1158
Asn Asn Gln Asp Gln Ser Ser Ser Leu Pro Glu Glu Cys Val Pro Ser
            360                 365                 370

gat gaa agt act cct ccg agt att aaa aaa atc ata cat gtg ctg gag   1206
Asp Glu Ser Thr Pro Pro Ser Ile Lys Lys Ile Ile His Val Leu Glu
        375                 380                 385

aag gtc cag tat ctt gaa caa gaa gta gaa gaa ttt gta gga aaa aag   1254
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BNSDOCID <WO 0014106A1 IA>

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Lys Val Gln Tyr Leu Glu Gln Glu Val Glu Glu Phe Val Gly Lys Lys
    390                 395                 400

aca gac aaa gca tac tgg ctt ctg gaa gaa atg cta acc aag gaa ctt   1302
Thr Asp Lys Ala Tyr Trp Leu Leu Glu Glu Met Leu Thr Lys Glu Leu
405                 410                 415                 420

ttg gaa ctg gat tca gtt gaa act ggg ggc cag gac tct gta cgg cag   1350
Leu Glu Leu Asp Ser Val Glu Thr Gly Gly Gln Asp Ser Val Arg Gln
                425                 430                 435

gcc aga aaa gag gct gtt tgt aag att cag gcc ata ctg gaa aaa tta   1398
Ala Arg Lys Glu Ala Val Cys Lys Ile Gln Ala Ile Leu Glu Lys Leu
            440                 445                 450

gaa aaa aaa gga tta tga aaggatttag aacaaagtgg aagcctgtta          1446
Glu Lys Lys Gly Leu
        455

ctaacttgac caaagaacac ttgattaggt taattaccct ctttttgaaa tgcctgttga 1506

tgacaagaag caatacattc cagcttttcc tttgatttta tacttgaaaa actggcaaag 1566

gaatggaaga atattttagt catgaagttg ttttcagttt tcagacgaat gaatgtaata 1626

ggaaactatg gagttaccaa tattgccaag tagactcact ccttaaaaaa tttatggata 1686

tctacaagct gcttattacc agcaggaggg aaacacactt cacacaacag gcttatcaga 1746

aacctaccag atgaaactgg atataatttg agacaaacag gatgtgtttt tttaaacatc 1806

tggatatctt gtcacatttt tgtacattgt gactgctttc aacatatact tcatgtgtaa 1866

ttatagctta gactttagcc ttcttggact tctgttttgt tttgttattt gcagtttaca 1926

aatatagtat tattctctaa aaaaaaaaaa aaaaaaaaaa                       1966


<210> 22
<211> 457
<212> PRT
<213> Homo sapiens

<400> 22
Met Ser Ala Leu Arg Arg Ser Gly Tyr Gly Pro Ser Asp Gly Pro Ser
  1               5                  10                  15

Tyr Gly Arg Tyr Tyr Gly Pro Gly Gly Gly Asp Val Pro Val His Pro
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BNSDOCID <WO 0014106A1 IA>

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            20                  25                  30

Pro Pro Pro Leu Tyr Pro Leu Arg Pro Glu Pro Pro Gln Pro Pro Ile
        35                  40                  45

Ser Trp Arg Val Arg Gly Gly Gly Pro Ala Glu Thr Thr Trp Leu Gly
    50                  55                  60

Glu Gly Gly Gly Gly Asp Gly Tyr Tyr Pro Ser Gly Gly Ala Trp Pro
65                  70                  75                  80

Glu Pro Gly Arg Ala Gly Gly Ser His Gln Glu Gln Pro Pro Tyr Pro
                85                  90                  95

Ser Tyr Asn Ser Asn Tyr Trp Asn Ser Thr Ala Arg Ser Arg Ala Pro
            100                 105                 110

Tyr Pro Ser Thr Tyr Pro Val Arg Pro Glu Leu Gln Gly Gln Ser Leu
        115                 120                 125

Asn Ser Tyr Thr Asn Gly Ala Tyr Gly Pro Thr Tyr Pro Pro Gly Pro
    130                 135                 140

Gly Ala Asn Thr Ala Ser Tyr Ser Gly Ala Tyr Tyr Ala Pro Gly Tyr
145                 150                 155                 160

Thr Gln Thr Ser Tyr Ser Thr Glu Val Pro Ser Thr Tyr Arg Ser Ser
                165                 170                 175

Gly Asn Ser Pro Thr Pro Val Ser Arg Trp Ile Tyr Pro Gln Gln Asp
            180                 185                 190

Cys Gln Thr Glu Ala Pro Pro Leu Arg Gly Gln Val Pro Gly Tyr Pro
        195                 200                 205

Pro Ser Gln Asn Pro Gly Met Thr Leu Pro His Tyr Pro Tyr Gly Asp
    210                 215                 220

Gly Asn Arg Ser Val Pro Gln Ser Gly Pro Thr Val Arg Pro Gln Glu
225                 230                 235                 240

Asp Ala Trp Ala Ser Pro Gly Ala Tyr Gly Met Gly Gly Arg Tyr Pro
                245                 250                 255

Trp Pro Ser Ser Ala Pro Ser Ala Pro Pro Gly Asn Leu Tyr Met Thr
            260                 265                 270

Glu Ser Thr Ser Pro Trp Pro Ser Ser Gly Ser Pro Gln Ser Pro Pro
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BNSDOCID <WO 0014106A1 A>

275 280 285

Ser Pro Pro Val Gln Gln Pro Lys Asp Ser Ser Tyr Pro Tyr Ser Gln
290 295 300

Ser Asp Gln Ser Met Asn Arg His Asn Phe Pro Cys Ser Val His Gln
305 310 315 320

Tyr Glu Ser Ser Gly Thr Val Ile Asn Glu Asp Ser Asp Leu Leu Asp
325 330 335

Ser Gln Val Gln Tyr Ser Ala Glu Pro Gln Leu Tyr Gly Asn Ala Thr
340 345 350

Ser Asp His Pro Asn Asn Gln Asp Gln Ser Ser Ser Leu Pro Glu Glu
355 360 365

Cys Val Pro Ser Asp Glu Ser Thr Pro Pro Ser Ile Lys Lys Ile Ile
370 375 380

His Val Leu Glu Lys Val Gln Tyr Leu Glu Gln Glu Val Glu Glu Phe
385 390 395 400

Val Gly Lys Lys Thr Asp Lys Ala Tyr Trp Leu Leu Glu Glu Met Leu
405 410 415

Thr Lys Glu Leu Leu Glu Leu Asp Ser Val Glu Thr Gly Gly Gln Asp
420 425 430

Ser Val Arg Gln Ala Arg Lys Glu Ala Val Cys Lys Ile Gln Ala Ile
435 440 445

Leu Glu Lys Leu Glu Lys Lys Gly Leu
450 455

<210> 23
<211> 4308
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (247)..(1590)

<400> 23
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BNSDOCID <WO 0014106A1 IA>

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ccctttcaccg gctgccccgc tcagacctag tcgggagggg tgcgaggcat gcagctgggg 120

gcccagctcc ggtgccgcac cccgtaaagg gctgatcttc cacctcgcca cctcagccac 180

gggacgccaa gaccgcatcc aattcagact tcttttggtg cttgtgaaac tgaacacaac 240

aaaagt atg gat atg gga aac caa cat cct tct att agt agg ctt cag    288
       Met Asp Met Gly Asn Gln His Pro Ser Ile Ser Arg Leu Gln
         1               5                  10

gaa atc caa aag gaa gta aaa agt gta gaa cag caa gtt atc ggc ttc   336
Glu Ile Gln Lys Glu Val Lys Ser Val Glu Gln Gln Val Ile Gly Phe
 15                  20                  25                  30

agt ggt ctg tca gat gac aag aat tac aag aaa ctg gag agg att cta   384
Ser Gly Leu Ser Asp Asp Lys Asn Tyr Lys Lys Leu Glu Arg Ile Leu
                 35                  40                  45

aca aaa cag ctt ttt gaa ata gac tct gta gat act gaa gga aaa gga   432
Thr Lys Gln Leu Phe Glu Ile Asp Ser Val Asp Thr Glu Gly Lys Gly
             50                  55                  60

gat att cag caa gct agg aag cgg gca gca cag gag aca gaa cgt ctt   480
Asp Ile Gln Gln Ala Arg Lys Arg Ala Ala Gln Glu Thr Glu Arg Leu
         65                  70                  75

ctc aaa gag ttg gag cag aat gca aac cac cca cac cgg att gaa ata   528
Leu Lys Glu Leu Glu Gln Asn Ala Asn His Pro His Arg Ile Glu Ile
     80                  85                  90

cag aac att ttt gag gaa gcc cag tcc ctc gtg aga gag aaa att gtg   576
Gln Asn Ile Phe Glu Glu Ala Gln Ser Leu Val Arg Glu Lys Ile Val
 95                  100                 105                 110

cca ttt tat aat gga ggc aac tgc gta act gat gag ttt gaa gaa ggc   624
Pro Phe Tyr Asn Gly Gly Asn Cys Val Thr Asp Glu Phe Glu Glu Gly
                115                 120                 125

atc caa gat atc att ctg agg ctg aca cat gtt aaa act gga gga aaa   672
Ile Gln Asp Ile Ile Leu Arg Leu Thr His Val Lys Thr Gly Gly Lys
            130                 135                 140

atc tcc ttg cgg aaa gca agg tat cac act tta acc aaa atc tgt gcg   720
Ile Ser Leu Arg Lys Ala Arg Tyr His Thr Leu Thr Lys Ile Cys Ala
        145                 150                 155

gtg caa gag ata atc gaa gac tgc atg aaa aag cag cct tcc ctg ccg   768
Val Gln Glu Ile Ile Glu Asp Cys Met Lys Lys Gln Pro Ser Leu Pro
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BNSDOCID <WO 0014106A1 !A>

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Leu Ser Glu Asp Ala His Pro Ser Val Ala Lys Ile Asn Phe Val Met
175                 180                 185                 190

tgt gag gtg aac aag gcc cga ggg gtc ctg att gca ctt ctg atg ggt   864
Cys Glu Val Asn Lys Ala Arg Gly Val Leu Ile Ala Leu Leu Met Gly
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gtg aac aac aat gag acc tgc agg cac tta tcc tgt gtg ctc tcg ggg   912
Val Asn Asn Asn Glu Thr Cys Arg His Leu Ser Cys Val Leu Ser Gly
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ctg atc gct gac ctg gat gct cta gat gtg tgc ggc cgg aca gaa atc   960
Leu Ile Ala Asp Leu Asp Ala Leu Asp Val Cys Gly Arg Thr Glu Ile
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aga aat tat cgg agg gag gta gta gaa gat atc aac aaa tta ttg aaa   1008
Arg Asn Tyr Arg Arg Glu Val Val Glu Asp Ile Asn Lys Leu Leu Lys
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tat ctg gat ttg gaa gag gaa gca gac aca act aaa gca ttt gac ctg   1056
Tyr Leu Asp Leu Glu Glu Glu Ala Asp Thr Thr Lys Ala Phe Asp Leu
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aga cag aat cat tcc att tta aaa ata gaa aag gtc ctc aag aga atg   1104
Arg Gln Asn His Ser Ile Leu Lys Ile Glu Lys Val Leu Lys Arg Met
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aga gaa ata aaa aat gaa ctt ctc caa gca caa aac cct tct gaa ttg   1152
Arg Glu Ile Lys Asn Glu Leu Leu Gln Ala Gln Asn Pro Ser Glu Leu
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tac ctg agc tcc aaa aca gaa ttg cag ggt tta att gga cag ttg gat   1200
Tyr Leu Ser Ser Lys Thr Glu Leu Gln Gly Leu Ile Gly Gln Leu Asp
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gag gta agt ctt gaa aaa aac ccc tgc atc cgg gaa gcc agg aga aga   1248
Glu Val Ser Leu Glu Lys Asn Pro Cys Ile Arg Glu Ala Arg Arg Arg
    320                 325                 330

gca gtg atc gag gtg caa act ctg atc aca tat att gac ttg aag gag   1296
Ala Val Ile Glu Val Gln Thr Leu Ile Thr Tyr Ile Asp Leu Lys Glu
335                 340                 345                 350

gcc ctt gag aaa aga aag ctg ttt gct tgt gag gag cac cca tcc cat   1344
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BNSDOCID <WO 0014106A1 IA>

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Lys Ala Val Trp Asn Val Leu Gly Asn Leu Ser Glu Ile Gln Gly Glu
            370                 375                 380

gtt ctt tca ttt gat gga aat cga acc gat aag aac tac atc cgg ctg  1440
Val Leu Ser Phe Asp Gly Asn Arg Thr Asp Lys Asn Tyr Ile Arg Leu
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gaa gag ctg ctc acc aag cag ctg cta gcc ctg gat gct gtt gat ccg  1488
Glu Glu Leu Leu Thr Lys Gln Leu Leu Ala Leu Asp Ala Val Asp Pro
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cag gga gaa gag aag tgt aag gct gcc agg aaa caa gct gtg agg ctt  1536
Gln Gly Glu Glu Lys Cys Lys Ala Ala Arg Lys Gln Ala Val Arg Leu
415                 420                 425                 430

gcg cag aat att ctc agc tat ctc gac ctg aaa tct gat gaa tgg gag  1584
Ala Gln Asn Ile Leu Ser Tyr Leu Asp Leu Lys Ser Asp Glu Trp Glu
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tac tga ataccagag atctcacttt tgatactgtt ttgcacttca tatgtgcttc    1640
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BNSDOCID <WO 0014106A1 IA>

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Leu Ser Asp Asp Lys Asn Tyr Lys Lys Leu Glu Arg Ile Leu Thr Lys
         35                  40                  45

Gln Leu Phe Glu Ile Asp Ser Val Asp Thr Glu Gly Lys Gly Asp Ile
     50                  55                  60

Gln Gln Ala Arg Lys Arg Ala Ala Gln Glu Thr Glu Arg Leu Leu Lys
 65                  70                  75                  80

Glu Leu Glu Gln Asn Ala Asn His Pro His Arg Ile Glu Ile Gln Asn
                 85                  90                  95

Ile Phe Glu Glu Ala Gln Ser Leu Val Arg Glu Lys Ile Val Pro Phe
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Tyr Asn Gly Gly Asn Cys Val Thr Asp Glu Phe Glu Glu Gly Ile Gln
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BNSDOCID: <WO 0014106A1_IA>

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Glu Ile Ile Glu Asp Cys Met Lys Lys Gln Pro Ser Leu Pro Leu Ser
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Glu Asp Ala His Pro Ser Val Ala Lys Ile Asn Phe Val Met Cys Glu
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Val Asn Lys Ala Arg Gly Val Leu Ile Ala Leu Leu Met Gly Val Asn
195 200 205

Asn Asn Glu Thr Cys Arg His Leu Ser Cys Val Leu Ser Gly Leu Ile
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225 230 235 240

Tyr Arg Arg Glu Val Val Glu Asp Ile Asn Lys Leu Leu Lys Tyr Leu
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Asp Leu Glu Glu Glu Ala Asp Thr Thr Lys Ala Phe Asp Leu Arg Gln
260 265 270

Asn His Ser Ile Leu Lys Ile Glu Lys Val Leu Lys Arg Met Arg Glu
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Ser Leu Glu Lys Asn Pro Cys Ile Arg Glu Ala Arg Arg Arg Ala Val
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Glu Lys Arg Lys Leu Phe Ala Cys Glu Glu His Pro Ser His Lys Ala
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Val Trp Asn Val Leu Gly Asn Leu Ser Glu Ile Gln Gly Glu Val Leu

BNSDOCID <WO 0014106A1 IA>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21053

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.. 1, 13, 24, 25
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

No meaningful search could be carried out because no limitations could be placed on the sequence.

3. ☐ Claims Nos.
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

BNSDOCID <WO 0014106A1 IA>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21053

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database Genbank, National Center for Biotech. Info., Accession No. G29287, MYERS, R.M., 04 October 1996, see entire reference.	2,4
X	Database Genbank, National Center for Biotech. Info., Accession No. G06974, HUDSON, T., "Whitehead Institute.MIT Center for Genome Research,'19 October 1995, see entire reference.	2,4
X	Database Genseq, Derwent, Alexandria, Virginia, Accession No. V81267, OTSUKA PHARM CO LTD, 'New Bcl-2 interaction prrtein gene (Bis)- useful for elucidation of the molecular mechanism of apoptosis, and in diagnosis, prevention and treatment of diseases,' 15 December 1998 see enire reference.	2-5
X	Database, Geneseq, Derwent, Alexandria, Virginia, Accession No. T19051, MATSUBARA ET AL., "Identifying gene signatures in 3'-directed human cDNA library,' 01 June 1995, see entire reference.	2,4
X	Database Geneseq, Derwent, Alexandria, Virginia, Accession No. Q90296, LA JOLLA CANCER RES FOUN. 'Human Bcl-2-associated protein BAG-1 cDNA,'18 May 1995 see entire reference.	2-5,14

BNSDOCID <WO 0014106A1 IA>

370 375 380

Ser Phe Asp Gly Asn Arg Thr Asp Lys Asn Tyr Ile Arg Leu Glu Glu
385 390 395 400

Leu Leu Thr Lys Gln Leu Leu Ala Leu Asp Ala Val Asp Pro Gln Gly
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Glu Glu Lys Cys Lys Ala Ala Arg Lys Gln Ala Val Arg Leu Ala Gln
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Asn Ile Leu Ser Tyr Leu Asp Leu Lys Ser Asp Glu Trp Glu Tyr
435 440 445

BNSDOCID <WO 0014106A1_'A>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21053

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :07N 21/02; C07K 1/00

US CL :530/387.1, 350; 435/6, 7/1; 536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/387.1, 350; 435/6, 7/1; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,652,223 A (KOHN ET AL) 29 July 1997(29/7/97) see entire document.	2-5, 14, 32-34
X	Database Genbank-EST, National Center for Biotech. Info., Accession No. AA693697, HILLIER, L. ET AL. 'WashU-NCI human EST Project,' 16 December 1997, see entire reference.	2
X	Database Genbank-EST, National Center for Biotech. Info., Accession No. AA456862, NCI_CGAP, 'National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index,' 15 August 1997, see entire reference.	2,4

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 24 NOVEMBER 1999	Date of mailing of the international search report 19 JAN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHEELA J. HUFF Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

BNSDOCID <WO 0014106A1 IA>